Neurology

OFFICIAL JOURNAL OF
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AUGUST--1960
Volume 10 - Number 8

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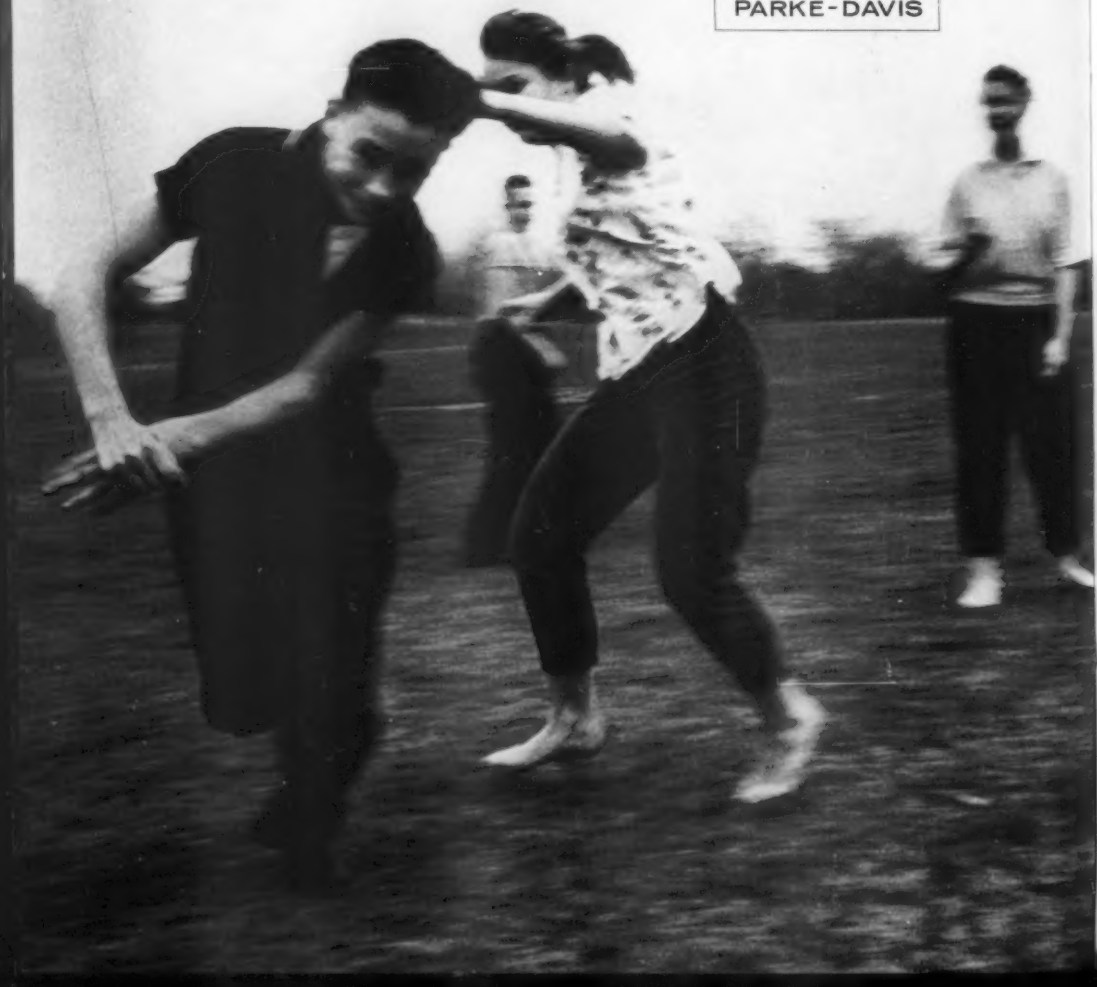

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°Livingston, S., and Petersen, D.: New England J. Med. **254**:327 (Feb. 16) 1956.

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Volume 10 **Neurology** *Number 8*

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AUGUST 1960 • *Contents*

A Cutaneous Disorder of Connective Tissue in Amyotrophic Lateral Sclerosis 717
HAROLD M. FULLMER, D.D.S., HOWARD D. SIEDLER, M.D., ROBERT S. KROOTH, M.D., Ph.D., AND LEONARD T. KURLAND, M.D.

Sensory Neuropathy with Ulcerative Mutilating Acropathy 725
MARY E. GRANGER, M.B., B.Ch.

Pathogenesis of Cerebral Vasospasm in Hypertensive Encephalopathy I. Effects of Acute Increases in Intraluminal Blood Pressure on Pial Blood Flow 735
JOHN S. MEYER, M.D., ARTHUR G. WALTZ, M.D., AND FUMIO GOTOH,, M.D.

A Simple Test of Coordination in the Fingers 745
C. MILLER FISHER, M.D.

Congenital Malformation of Spinal Canal with Neurogenic Bladder 747
PAUL B. JOSSMANN, M.D., Ph.D., JOSEPH FISCHMANN, M.D., F.A.C.S., AND CESAR G. TEDESCHI, M.D.

Value of Equivocal Signs in Neurologic Diagnosis 753
MARGARET A. KENNARD, M.D.

Case Report: Sudanophilic Leukodystrophy with Increased Hexosamine Content 765
P. J. DYCK, M.D., J. N. CUMINGS, M.D., AND J. OLSZEWSKI, M.D.

Treatment of Malignant Brain Tumors with Alkylating Agents 772
VERNON H. MARK, M.D., RAYMOND N. KJELLBERG, M.D., ROBERT G. OJEMANN, M.D., AND ALBERT H. SOLOWAY, Ph.D.

(Continued on next page)

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Contents—*Continued*

Usefulness of Photic Stimulation in Routine Clinical Electroencephalography 777
JOHN R. HUGHES, M.A., Ph.D.

Arachnoidal Cyst of the Cisterna Ambiens 783
AKIHUMI KATAGIRI, M.D.

Case Report: Convulsive Seizures as the Presenting Manifestation of Intermittent Porphyria 787
JONATHAN D. WIRTSCHAFTER, M.D., FRED W. TURNER, M.D., AND ROBERT S. DOW, M.D.

Case Report: Myasthenia Gravis in One Monozygotic Twin 793
MILTON ALTER, M.D., AND O. RHETT TALBERT, M.D.

Case Report: Significance of Amplitude Asymmetry in the Electroencephalogram 799
ROBERT J. STROBOS, M.D.

Book Reviews 804

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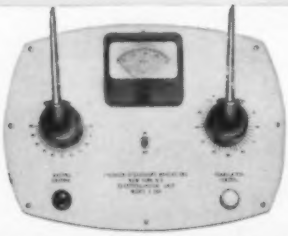

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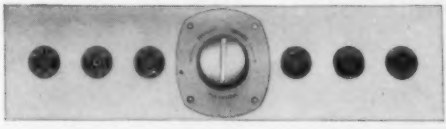

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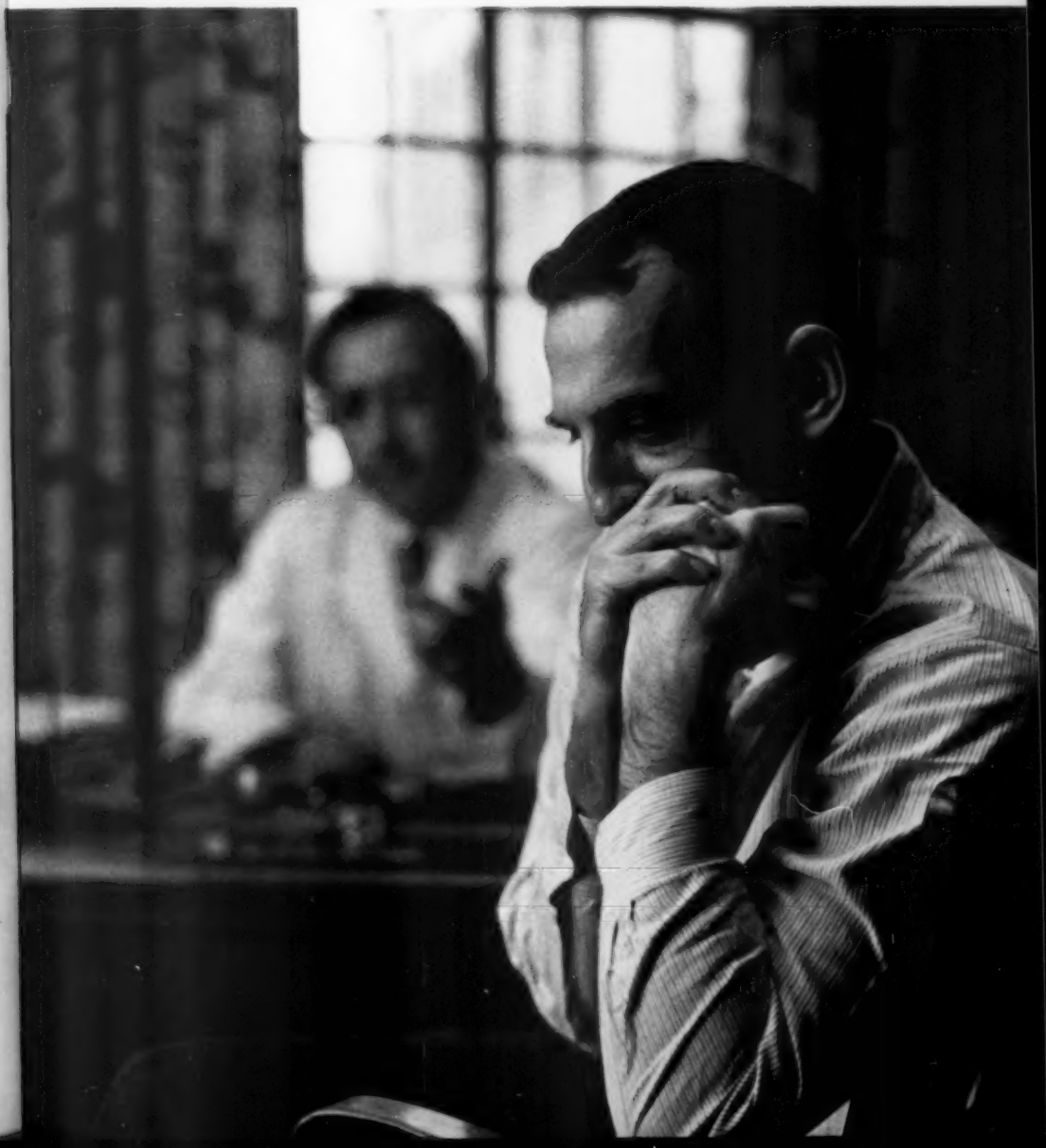

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. et al.: *J.A.M.A. 160*:348 (Feb. 4) 1956.

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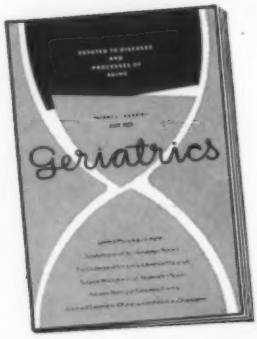

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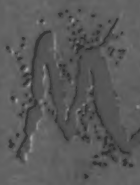

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*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders, J.A.M.A. 170:1263, July 11, 1959.

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

Neurology Volume 10 • Number 8

A cutaneous disorder of connective tissue in amyotrophic lateral sclerosis

A histochemical study

Harold M. Fullmer, D.D.S., Howard D. Siedler, M.D.,
Robert S. Krooth, M.D., Ph.D., and Leonard T. Kurland, M.D.

AMYOTROPHIC lateral sclerosis (ALS) has recently been shown to be exceedingly prevalent on Guam.[1-4] Whether the pathogenesis of ALS in Guam, which accounts for 10% of all deaths among adults, is the same as elsewhere has not yet been determined.

During the course of a comparative histochemical study (unrelated to ALS) of connective tissues from various sites, a curious disorder was found in the connective tissues of the abdominal skin taken at autopsy from a person with ALS. Hematoxylin and eosin preparations revealed a thickened papillary layer that stained very faintly with eosin. Although some pathologists agreed that this characteristic might represent an abnormal condition, others considered it to be within normal limits of variation. Azure A revealed no metachromatic material in the skin, which thus indicates a lack of acid mucopolysaccharides. However, sections stained by the recently described peracetic acid–aldehyde fuchsin–Halmi method[5-7] revealed mucopolysaccharides throughout the entire dermis greatly in excess of normal. A histochemical examination of skin from other patients with ALS revealed additional abnormalities of connective tissue. A study of deltoid and abdominal skin biopsies from a large number of patients with ALS or other diseases was then initiated. The results of this investigation are the subject of this report.

MATERIALS AND METHODS

Biopsy specimens of abdominal or deltoid skin were obtained by the use of either a 6-mm. key punch or a scalpel. Of the 46 ALS cases, 26 were from Guam and 20 from the continental United States; 15 cutaneous biopsies were obtained from healthy persons and 58 from patients with other diseases. The specimens were fixed in Lillie's aqueous neutral calcium acetate 10% formalin,[8] dehydrated, embedded in paraffin, and sectioned at 6μ.

Staining reactions and enzymatic digestions. Several sections from each biopsy were stained

From the National Institute of Dental Research and the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

by the peracetic acid–aldehyde fuchsin–Halmi staining method.[6] Sections stained by this method should be examined within a few days, since considerable fading was noted after a few weeks. Unstained sections were also noted to stain less intensely after storage than did the original sections from the same block. Sections from a few patients with ALS that were stained with azure A (0.5% concentration in aqueous 0.2 M phosphate buffer at *p*H 4 for ten minutes at 25° C.) and with Rinehart's dialyzed iron–picrofuchsin stain[8] did not demonstrate any specific variation in this disease, and use of these stains was discontinued. The periodic acid–Schiff stain was carried out as described by Lillie.[8] In the enzymatic digestion studies, testicular hyaluronidase (Nutritional Biochemicals Corp.) was used 1:1,000 in 0.1 M phosphate buffer for twenty-four hours at 37° C., β-glucuronidase (Nutritional Biochemicals Corp.) was used 15 mg. per 50 cc. in 0.1 M acetate buffer at *p*H 4.5 for twenty-four hours at 37° C., and lysozyme (Worthington Biochemicals Corp.) was used 5 mg. per 30 cc. in 0.2 M phosphate buffer at *p*H 5.3 for twenty-four to seventy-two hours at 37° C. A few milligrams of penicillin and streptomycin were added to the enzyme incubation mixtures to prohibit the growth of microorganisms.

Microscopic examinations of dermal biopsies from persons without known disease and with ALS and other diseases were performed. Certain abnormalities, to be described further below, which were frequently found in ALS patients, were selected as criteria for the histologic diagnosis of ALS. In general, these abnormalities were altered carbohydrate (including mucopolysaccharide) content of the skin, characteristic elastosis, and alterations of collagen morphology and apparent turnover. Dermal biopsies from persons known to have ALS or other diseases and healthy volunteers were then referred to one of us for microscopic analysis. The microscopist had no knowledge of the origin of the specimens. About 6 sections from each specimen were studied, and the information from all sections was pooled to determine the diagnosis.

A biopsy was considered "diagnostic" of ALS if it had several of the changes listed below and, "not ALS" if it had none of the changes listed below. (Use of the term "diagnostic" in this text implies only the presence of certain abnormal histologic variations, listed in the results section, observed in dermal biopsies of a certain percentage of patients with ALS. It does not imply that these criteria are diagnostic of ALS. Further investigations are required to determine the usefulness of these criteria as a diagnostic agent.) A biopsy was read as "questionable" if it contained changes suggestive but insufficiently diagnostic of ALS. Cases were classified into 3 categories after microscopic studies were completed and compared with clinical diagnosis.

RESULTS

A critical analysis of the dermal biopsies from 46 patients with ALS, and 69 persons with other diseases and healthy volunteers indicated that a high proportion of ALS patients had characteristic changes in the dermis. Figures 1 and 2 are sections from normal individuals stained with the peracetic acid–aldehyde fuchsin–Halmi method. Figures 3 through 15 are sections of skin from several cases of ALS, stained with the same method, illustrating some of the alterations of connective tissues found in ALS.

The characteristic features of the dermal disorder in ALS patients are best demonstrated by the peracetic acid–aldehyde fuchsin–Halmi staining method and consist of:

1] An elastosis (Figs. 3 and 4) that is distinguishable from basophilic degeneration or so-called senile elastosis by the absence of homogeneous masses of modified elastic (or collagenous) material reactive with all elastic tissue stains

2] An increased amount of mucopolysaccharide throughout the dermis (Figs. 3 through 5)

3] Degeneration of the arrector pili muscles manifested by an elastosis that appears to begin distally and progresses proximally; vacuolization may be observed in these muscles, and the outer cortical portion appears to imbibe mucopolysaccharide and undergo elastosis before this change occurs internally (Figs. 3 and 4)

4] Focal areas of altered connective tissues which, on the basis of morphology and staining reactions, appear to have been regenerated

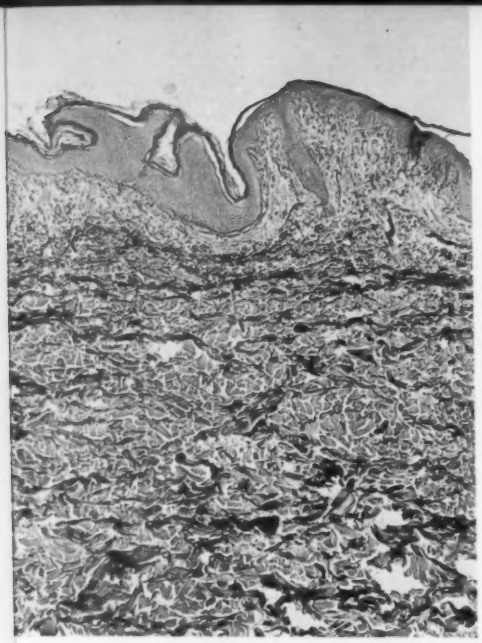

Figure 1

Figure 2

All sections were stained with the peracetic acid–aldehyde fuchsin–Halmi stain. Collagen stains green. Elastic fibers, mucopolysaccharides, and hair shafts stain purple. Keratin stains purplish-red.

Fig. 1. Section of normal abdominal skin from a 19-year-old man. × 65

Fig. 2. Section of normal abdominal skin from a 59-year-old woman. × 35

Figs. 3 and 4. Sections of deltoid skin from a 46-year-old man with ALS. Note generalized elastosis, elastosis and degeneration of the arrector pili muscles, and increased mucopolysaccharides throughout the dermis. × 87 and × 55

Figure 3

Figure 4

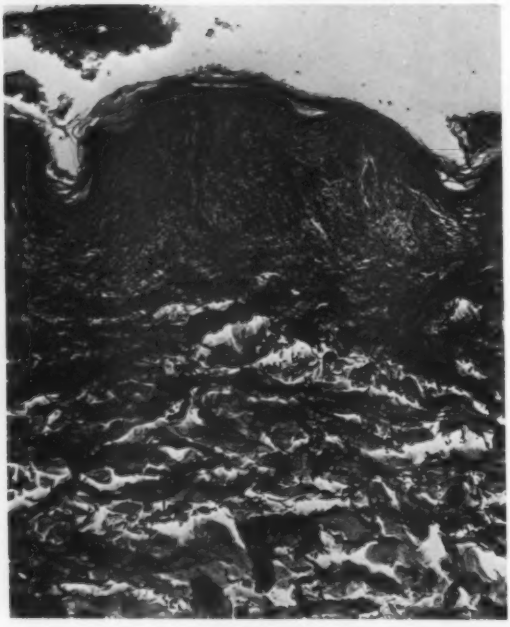

Figure 5

Fig. 5. Section of abdominal skin from a 38-year-old man with ALS. The altered staining of collagen is believed to be due to an altered collagen composition. × 87

Figure 6

Fig. 6. Section of deltoid skin from a 46-year-old man with ALS. Note that the outlined area between the 2 muscles apparently has been regenerated. The collagen bundles and elastic fibers are very small. × 31

Figure 7

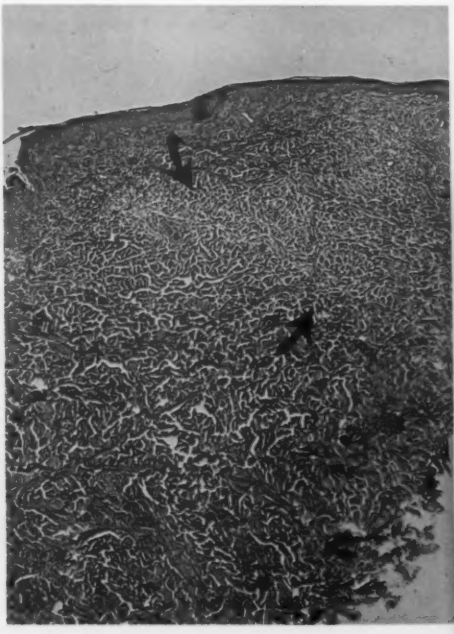

Fig. 7. Section of abdominal skin from a 48-year-old woman with ALS. Note that the outlined area apparently has been regenerated. × 30

Figure 8

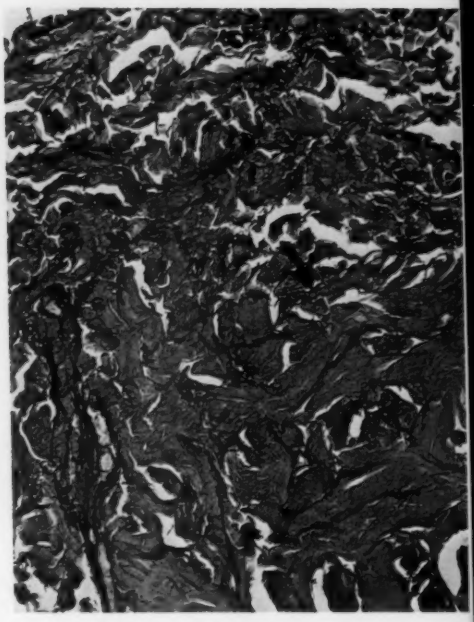

Figure 9

Figs. 8 and 9. Sections of abdominal skin from a 53-year-old man with ALS. Note the area, indicated by the arrow, within the more normal connective tissues which contains unduly large collagen bundles. Mucopolysaccharide is also increased throughout. × 22 and × 55

Fig. 10. Section of deltoid skin from a 43-year-old woman with ALS. The photomicrograph illustrates a generalized disorientation of the connective tissues. × 36

Figure 10

Figure 11

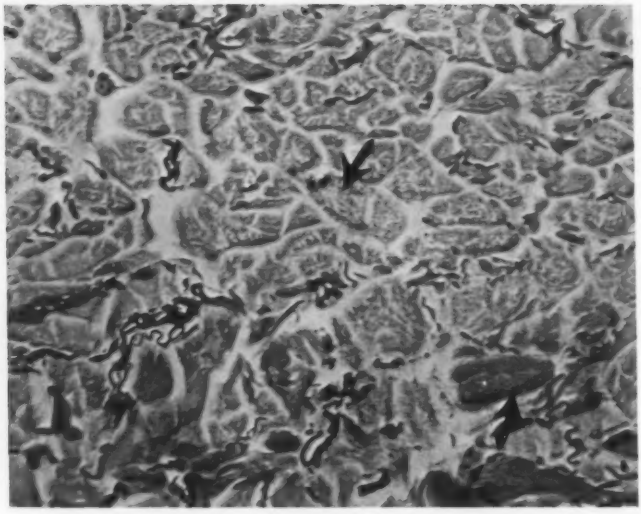

Figure 12

Figs. 11 and 12. Sections of abdominal skin from a 59-year-old woman with ALS. The arrow in Figure 11 and the lowest arrow in Figure 12 point to the same normal bundle of collagen. The other arrow in Figure 12 points to a bundle of collagen, the interior of which appears to have undergone solution. × 55 and × 245

Fig. 13. Section of deltoid skin from a 45-year-old woman with ALS, demonstrating fragile elastic and collagen fibers that fragment upon sectioning. × 55

Figure 13

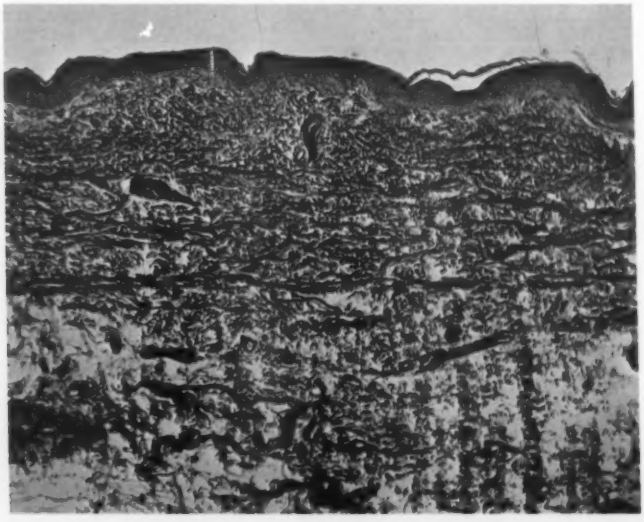

TABLE 1
HISTOLOGIC REVIEW OF CONNECTIVE TISSUE CHANGES FOUND IN SKIN BIOPSIES FROM PATIENTS WITH ALS

	Source	Number	Number*			Per cent		
			Changes present	Questionable	Absent	Changes present	Questionable	Absent
BIOPSIES	Guam	34	21	9	4	62	26	12
	United States	23	10	4	9	43	17	39
	Total	57	32	13	13	56	23	23
PATIENTS	Guam	26	18	6	2	69	23	8
	United States	20	9	4	7	45	20	35
	Total	46	27	10	9	59	22	20

*When more than one skin biopsy specimen from an ALS patient was available, the results of the microscopic review by patient were placed in the "changes present" category if at least one specimen was read as characteristic of ALS, in the "questionable" group if no specimens were diagnostic and at least one was questionable, and in the "absent" group if all sections were read as not ALS.

within apparently normal connective tissues (Figs. 6 and 7).

5] Altered collagen manifested in several ways: [A] collagen bundles that are more homogeneous and opaque and retain more stain than normal (Fig.5); [B] areas of unduly large, coarse collagen bundles that may or may not contain degenerative elastic tissue (Figs. 8 and 9); [C] disorientation of collagen bundles and elastic fibers that may also show structural alterations (Fig. 10); [D] focal areas of collagen bundles that are apparently undergoing dissolution (Figs. 11 and 12); and [E] fragile collagen and elastic fibers that fragment upon sectioning (Fig. 13). Hence, the dermis in ALS patients presents a variable pattern.

No single section or biopsy contained all the variations listed above, but several changes were usually found. Some of the alterations are regarded as being more diagnostic of ALS than others. For example, although the elastosis and arrector pili muscle changes are characteristically associated with ALS, they may also be found in the dermis of aged persons without this disease. Also, although mucopolysaccharide as revealed by the peracetic acid–aldehyde fuchsin–Halmi stain was characteristically increased in ALS patients, the dermis of some healthy persons and patients with other diseases had increased amounts of mucopolysaccharide. The changes ascribed to collagen, listed under 4 and 5 above, are regarded as the most characteristic and are adjudged diagnostic of ALS when the alterations are sufficiently bizarre, such as in Figures 6 through 13.

Tables 1 and 2 contain the results of the microscopic analysis, using the connective tissue variations listed above as the diagnostic criteria. As can be seen, almost 60% of the ALS patients examined in this investigation had the characteristic connective tissue changes in the dermis. Table 2 indicates that all skin biopsies obtained from healthy persons and patients with other diseases who resided in the United States did not have sufficient changes to suggest the diagnosis of ALS, although it is presumed that some will be found. Some non-ALS patients from Guam did have dermal changes indistinguishable from those seen in patients with ALS. Biopsies from 2 Guamanians with parkinsonism and 3 "healthy" Guamanian volunteers had connective tissue changes particularly suggestive of those seen in ALS. Table 2 also gives the clinical diagnoses in patients contributing biopsies to the non-ALS group.

Special note should be taken of 2 patients with ALS who had multiple biopsies; one had the characteristic changes of ALS in the abdominal skin, whereas the deltoid skin appeared normal. The other had characteristic changes in the deltoid skin and normal-appearing abdominal skin.

Correlation of clinical features and biopsy results from ALS patients. We have recently

TABLE 2

CLINICAL DIAGNOSES IN 70 BIOPSIED PATIENTS WITHOUT ALS AND RESULTS OF HISTOLOGIC REVIEW OF SPECIMENS

Source	Diagnosis	Results of Histologic Review: Not ALS	Questionable	Changes found in ALS patients
United States	Normal	4	–	–
	Inguinal hernia	3	–	–
	Cholecystitis	1	–	–
	Ovarian dysfunction	1	–	–
	Psychosis	3	–	–
	Cancer	7	–	–
	Headaches	1	–	–
	Syncope	1	–	–
	Seizures	2	–	–
	Diabetes and hypertension	1	–	–
	Diabetes with neuropathy	1	–	–
	Multiple sclerosis	4	–	–
	Tabes dorsalis	1	–	–
	Cervical arthritis	1	–	–
	Primary lateral sclerosis	1	–	–
	Peroneal muscular atrophy	2	–	–
	Hereditary spinal muscle atrophy (duration, 20 years)	1	–	–
	Syringomyelia	2	–	–
	Parkinsonism	1	–	–
	Huntington's chorea	1	–	–
	Thoracic cord injury	1	–	–
	Myotonia dystrophica	1	–	–
	Cervical cord injury (with muscle atrophy at biopsy site†)	2	–	–
	Cervical cord tumor (with muscle atrophy at biopsy site†)	1	–	–
	Acute porphyria (with muscle atrophy at biopsy site†)	1	–	–
	Postinfectious neuronitis (with muscle atrophy at biopsy site†)	1	–	–
	Brachial neuritis (with muscle atrophy at biopsy site†)	1	–	–
	Brachial plexus injury (with muscle atrophy at biopsy site†)	1	–	–
	Postpoliomyelitis (with muscle atrophy at biopsy site†)	1	–	–
	Peroneal muscular atrophy (with muscle atrophy at biopsy site†)	1	–	–
	Number	50		

		Not ALS	Questionable	Changes found in ALS patients
Guam	Normal	8	–	3
	Inguinal hernia	1	–	–
	Small bowel obstruction	1	–	–
	Transfusion reaction	–	1	–
	Parkinsonism	5	2	2
	Number	15	3	5
	Total Number	65	3	5
	Per cent	89	4	7

*73 biopsies from 70 patients; 2 parkinsonism patients from Guam each had 2 biopsies. Both specimens from 1 patient were read as "not present," and 1 specimen from the other patient was read "not present" and 1 "questionable." A U. S. patient was biopsied at cholecystectomy and later at inguinal herniorrhaphy.

†All the patients in this group had active or recent (within six months) muscle atrophy except the patient with cervical cord tumor and the patient with postpoliomyelitis.

Hirano and Malamud noted neurofibrillary changes common to both ALS and "parkinsonism" cases on Guam. All "parkinsonism" cases had concomitant presenile dementia. Of 27 cases observed by Hirano, 12 also had signs and symptoms of motor neurone involvement; 5 of these had both upper and lower motor neurone and 7 had upper motor neurone involvement. (Unpublished data)

TABLE 3

MEAN AGES OF ALS PATIENTS BY RESULTS OF HISTOLOGIC REVIEW OF SPECIMENS AND BY ORIGIN

Age	United States*			Guam			Total		
	Changes present	*Questionable*	*Absent*	*Changes present*	*Questionable*	*Absent*	*Changes present*	*Questionable*	*Absent*
0- 9	–	–	–	–	–	–	–	–	–
10-19	–	–	–	–	–	–	–	–	–
20-29	–	–	–	2	1	–	2	1	–
30-39	3	1	1	1	1	–	4	2	1
40-49	1	–	4	10	4	4	11	4	8
50-59	2	1	3	5	1	–	7	2	3
60-69	2	1	1	3	2	–	5	3	1
70-79	–	1	–	–	–	–	–	1	–
Total	8	4	9	21	9	4	29	13	13
Mean age by histologic criteria	52.0	57.3	48.8	48.2	46.3	44.0	49.3	49.7	47.3
Mean age by origin		51.6			47.2			48.9	
Mean ages of non-ALS groups		40.2			38.9			39.8	

*Age unknown for 1 U. S. patient with 2 diagnostic biopsies

TABLE 4

RESULTS OF HISTOLOGIC REVIEW OF SPECIMENS FROM ALS PATIENTS BY CLINICAL STATUS OF DISEASE* AND ORIGIN

	UNITED STATES							GUAM						
	Changes present		*Questionable*		*Absent*		*Total*	*Changes present*		*Questionable*		*Absent*		*Total*
Stage of disease	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.
Mild to moderately advanced	4	29	3	21	7	50	14	4	67	2	33	–	–	6
Severe	4	67	1	17	1	17	6	8	57	2	14	4	29	14

*This is naturally an arbitrary classification, and information on a number of patients was incomplete.

begun to inquire into the correlation between certain features of the disease and the biopsy results, although detailed clinical information was not available for all our patients. We have thus far specifically considered the influence of the patients' age, severity of affection, national origin, and sex. The term "severity" refers to a clinical impression of both the number of involved muscles and the extent to which they are involved. We do not at present have sufficient data to examine the 2 facets of progression of the disease separately. We shall now consider these 4 factors in turn.

In Table 3, the specimens are tabulated simultaneously by age of the patient and histologic category. As can be seen, there is little correlation between age and histologic category except for a very slight tendency for older patients to fall into the diagnostic group. However, this effect may be due largely to the fact that, on the average, older patients tend to have slightly more advanced disease, if only because one is including patients who have had the disease for a longer period of time.

In Table 4, the specimens are tabulated by both histologic category and stage of the dis-

TABLE 5

RESULTS OF HISTOLOGIC REVIEW OF SPECIMENS FROM PATIENTS WITH ALS BY SEX AND BY ORIGIN

	MALE						FEMALE					
	Changes present		*Questionable*		*Absent*		*Changes present*		*Questionable*		*Absent*	
Origin	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Guam	8	50	6	38	2	13	12	71	3	18	2	12
U. S.	5	31	4	25	7	44	5	71	–	–	2	29
Total	13	41	10	31	9	28	17	71	3	13	4	17

TABLE 6

SEVERITY OF DISEASE BY SEX AND ORIGIN

	U. S.		Guam	
	Male	*Female*	*Male*	*Female*
Mild to moderately advanced	10	4	3	3
Severe	4	2	4	10
Total	14 (70%)	6 (30%)	7 (35%)	13 (65%)

TABLE 7

BIOPSIES BY SEVERITY OF DISEASE, DIAGNOSTIC CATEGORY, AND SEX

Total	*Change present*	*Questionable*	*Absent*	*Total*
		MALE		
Mild to moderately advanced	3	5	5	13
Severe	4	1	3	8
Total	7	6	8	21
		FEMALE		
Mild to moderately advanced	5	0	2	7
Severe	8	2	2	12
Total	13	2	4	19

ease. In the U. S. material, the severely affected patients clearly tend to have specimens in the diagnostic category more commonly than do patients with mild or moderately advanced disease. For example, the ratio of diagnosable specimens is 4:7 in the mild-to-moderate U. S. group, whereas it is 4:1 in the severely affected U. S. group.

Table 1 indicates that the Guam patients had specimens in the diagnosed group more commonly than did the U. S. patients. The diagnosable ratio is 5:1 for Guam and about 1:1 for the U. S. Table 4, however, shows that the Guam series is considerably richer in severely affected patients and, moreover, reveals essentially no correlation between histologic category and origin of patients among the severely affected. Among more mildly affected patients, the over-all correlation persists, but one suspects that, within this group,

the Guam material included more persons with advanced disease. Therefore, we favor the view that the origin of patients has no independent influence on the histologic findings.

In Table 5, the specimens are tabulated simultaneously by the patient's sex, origin, and histologic category. The diagnosable ratio is about 4:3 for males and 4:1 for females. Table 6, however, suggests that, at least for Guam, females were proportionately more severely affected than males. Table 7 suggests that the sex effect persists when severity of affection is held constant, but one cannot be sure that the sex difference in the histologic classification of specimens does not reflect only the more advanced disease of the females. The numbers we are dealing with here are quite small and have large sampling errors.

In summary, it may be said that the probability of correctly diagnosing a skin specimen from an ALS patient seems to be influenced by the severity of the patient's disease. Specimens from female patients may lead to a correct diagnosis more frequently than do those from males, but we cannot separate this effect from the influence of severity.

Results of other stains and digestion experiments. The dermis of most patients with ALS reacted more strongly than normal with the periodic acid–Schiff stain, and the epidermal epithelial cells were usually laden with glycogen. A twenty-four-hour digestion with either testicular hyaluronidase or β-glucuronidase removed all mucopolysaccharides stainable with the peracetic acid–aldehyde fuchsin–Halmi method from the dermis of patients with ALS. A seventy-two-hour digestion with lysozyme was without effect on the subsequent peracetic acid–aldehyde fuchsin–Halmi staining reaction.

DISCUSSION

By the use of the peracetic acid–aldehyde fuchsin–Halmi stain, bizarre alterations of connective tissues were discovered for the first time in the dermis of patients with amyotrophic lateral sclerosis. On gross examination, the skin of these patients appears normal. The observations of an altered carbohydrate (including mucopolysaccharide) content of the skin elastosis, and alterations of collagen morphology and apparent turnover in some areas favor a basic defect of connective tissue cells in at least some ALS patients.

No evidence exists that a peculiar type of mucopolysaccharide is produced in this disease, since it is digested by either testicular hyaluronidase or β-glucuronidase but not by lysozyme, just as is the case in normal skin sections. However, the dermal connective tissue of most ALS patients possesses excessive amounts of carbohydrate, as seen in periodic acid-Schiff preparations. Also, the epidermal cells seem to contain more glycogen than normal; however, this observation is not proved. These findings suggest the possibility of a defect in carbohydrate metabolism of connective tissue and epidermal cells.

The observations that an examination of several sections aids in establishing a diagnosis and that the characteristic changes may be found in the deltoid and not abdominal sections, or vice versa, indicate that the connective tissue alterations described above are not uniform throughout the entire dermis. Since the changes are not uniform and the diagnosis of ALS could be inferred from skin sections more readily in persons with advanced disease, it may be presumed that the skin changes begin at a few sites, with more areas becoming involved as the disease progresses. Alternatively, a few areas may grow progressively more abnormal as the disease advances. At present, we cannot distinguish between these two possibilities.

As the distinctive connective tissue changes in patients with ALS were recognized, the question arose as to whether they represented a primary pathologic characteristic of the disease or are a manifestation of a loss of innervation to the segments studied. Included in the non-ALS group were 9 patients from the continental United States who had in the biopsied area wasting muscles due to a variety of neurologic lesions. None of these patients had skin changes suggestive of those seen in patients with ALS. The neurologic disease processes or injuries in 7 of these 9 patients had either occurred or were active within the six months preceding the date the biopsies were taken; 3 additional biopsies from skin overlying atrophied muscle have been found

to be negative (Table 2). These specimens included calf biopsies from a patient with a herniated lumbar disk and a postpoliomyelitis patient and a forearm biopsy from a patient with possible syringomyelia. These specimens are not in the statistics because the biopsy sites were other than abdominal or deltoid.

Specimens from 3 infants with infantile muscular atrophy (Werdnig-Hoffmann disease) were also examined. These sections manifested the characteristic elastosis of infants but failed to demonstrate the connective tissue changes that are the subject of this report. These patients were not included in the statistics because of their age. Although more observations are surely needed to clarify the relationship of the described skin changes to the neurologic features of ALS, these preliminary data suggest that the changes are not secondary to local nerve or cord lesions.

We are, however, concerned with ruling out the possibility that the degenerative and regenerative changes in these specimens is related to readjustments of the skin to the diminishing muscle mass beneath it.

Abdominal skins from 2 patients having scleroderma were available for study during the course of these investigations. The first specimen had the characteristic abundance of hard, sclerotic hyalinized collagen with no apparent alteration of mucopolysaccharides or elastic fibers, thereby bearing no resemblance to the dermis of ALS patients. The other specimen was obtained at the time of autopsy from a 21-year-old colored woman whose abdominal muscles were atrophied and scarred beneath the skin taken for examination. The muscle atrophy in this disease is presumed to be secondary to connective tissue changes.[9] Her peripheral nerves had also undergone sclerosis. Sections from this skin presented evidence of active collagen formation reminiscent of some areas in sections from patients with ALS, although the bizarre alterations of collagen distinctive of ALS patients were missing.

Biopsies were obtained from 2 United States patients who gave histories of other family members affected with ALS; 1 of these patients with an affected brother had 2 abdominal biopsies. Both specimens appeared to be normal. The other patient gave a history of 17 affected members in 7 generations.[10] The biopsy from this patient was also considered normal. These limited observations are not sufficient to indicate whether skin changes will be found in patients who have the familial form of ALS. If the typical changes are found in these patients, biopsies must be obtained from other family members to determine if the skin changes sometimes are present in the absence of detectable neurologic disease.

SUMMARY

A disorder of connective tissue in the dermis of about 60% of patients suffering from amyotrophic lateral sclerosis has been described. The disorder consists of [1] a distinctive elastosis, [2] an increase of mucopolysaccharide, [3] a degeneration and elastosis of arrector pili muscles, [4] focal areas of regenerated connective tissues, and [5] alterations of collagen. These changes were found in a number of patients from the United States and Guam. Patients severely afflicted with ALS manifest the disorder more often than those less affected.

Persons without known disease and those with various diseases residing in the continental United States had none of these changes in their skin biopsies; however, some Guamanians without known disease and some affected with parkinsonism had dermal alterations indistinguishable from those ascribed to ALS.

Photographs courtesy of Mr. John W. McGuire

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Sensory neuropathy with ulcerative mutilating acropathy

An isolated case

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ULCERATIVE MUTILATING ACROPATHY was a phrase used by Thévenard[1] to describe a strange disease that had intrigued physicians for nearly a century. The disease was characterized by skin ulceration, osteolysis, and definite dissociative anesthesia of the extremities with frequent loss of supinator and Achilles jerks. Progression of the disease often resulted in a mutilated appearance of the extremities resembling leprosy. Sporadic and familial cases were reported, and both types showed an almost stereotyped symptomatology.

The earliest complete study of the disease is that of Leplat,[2] who described it in 1846 under the title "Mal perforant du pied." Nélaton[3] reviewed the disorder and reported the case of a patient with 2 affected and 3 unaffected brothers. His patient had blistering, skin ulceration, and osteolysis of the feet necessitating multiple amputations without the need for chloroform. Nélaton observed local anesthesia at the site of the lesions. He described in perfect detail the progression of the disease, mentioning the occurrence of occasional transient blisters of the hands. The etiology of the disease was unknown to him.

Since then, an extensive literature on the subject has grown up, the consensus being that the disease was probably lumbosacral syringomyelia.[4–9] Another school of thought ascribed the disorder to faulty closure of the neural tube, using such terms as myelodysplasia[10] and status dysraphicus.[11]

Hicks,[12] in 1922, described a hereditary disease the main features of which were perforating ulcers of the feet, shooting pains in various parts of the body, and deafness. He recorded loss of ankle jerks, failure to elicit a plantar response, and loss of sensation over the feet, pain and temperature being lost over a rather larger area than light touch, so that there was definite dissociative anesthesia. He stated that the disease bore some resemblance to syringomyelia but was unable to completely reconcile the symptoms with those of that disease, of any recognized hereditary nervous disease, or of any disease known to cause perforating ulcers.

Smith[13] described "an unusual condition" in two generations of a family characterized by foot ulceration with anesthesia and loss of bone. He, like Hicks, was convinced that the disease was not syringomyelia.

In 1944, van Bogaert was at a clinical meeting with neurologists of the British Army in Belgium. Among the cases discussed was that of a patient with ulcerative mutilating acropathy with deafness, who had two brothers with an almost similar disorder. Dr. M. J. McArdle told the meeting that he had seen a similar case in 1936 with Denny-Brown, who had shown that the disease was not syringomyelia but primary degeneration of the dorsal spinal ganglia and posterior nerve roots. Moreover, he remarked that Denny-Brown's patient was also deaf. Van Bogaert was able to perform autopsy studies on his patient in 1947 but did not publish his findings until 1953,[14] after Denny-Brown recorded his in 1951.[15]

The case studied by Denny-Brown and

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McArdle in 1936 was a female member of the family previously described by Hicks in 1922. At autopsy, the absence of myelodysplasia or syringomyelia was proved with certainty and the essential lesion shown to be primary degeneration of the dorsal root ganglia with degeneration of the dorsal columns of the lumbar portion of the spinal cord, dorsal nerve roots, and peripheral nerves. Attention was drawn to deposits of a hyaline substance in the dorsal ganglia together with amyloid degeneration of the small blood vessels in the ganglia. In 1951, Denny-Brown published these findings under the title "Hereditary sensory radicular neuropathy" and was the first person to provide pathologic proof of the radicular nature of ulcerative mutilating acropathy.

In his case, van Bogaert also observed lesions of the dorsal root ganglia and dorsal nerve roots, much less severe lesions of the nerve trunks, and more marked lesions of the peripheral nervous system. He also was able to demonstrate deposits of a hyaline substance in the ganglia and blood vessels of the ganglia. In the muscles, skin, and aponeuroses of an affected foot, the nerves showed important cylindraxial rarefaction with perineural fibrosis and there was dense adventitious fibrosis of the vascular network. He found atrophic lesions of muscle, which were neural in origin.

Sporadic cases of ulcerative mutilating acropathy have not been so well documented. Kienböck[16] collected 21 cases and described the characteristics perfectly but did not realize the nature of the disorder. In 1951, 3 sporadic cases with identical features were briefly described by Denny-Brown. Thévenard[17] did not report sporadic cases because he thought that the absence of proven etiology and anatomic study deprived them of much of their interest. Van Bogaert[18] was of the opinion that sporadic cases occurred more commonly than familial but that their symptomatology was neither as typical nor as striking.

The case described here is in some respects atypical but is certainly striking.

CASE REPORT

B.T., a 57-year-old woman, was admitted to the Cardiff Royal Infirmary under the care of Dr. J. D. Spillane in July 1959.

She had been unduly sensitive to cold since childhood, and her hands, the left in particular, and feet became numb and purple in cold weather. During her late twenties, she became subect to painful, slowly healing, recurrent ulcers of the mouth and tongue.

In 1940, when she was 38 years old, a clear, painful blister developed overnight on the dorsum of her right foot and there was no known causative trauma. The blister burst to expose a raw, painful ulcer that healed in two months. A similar blister appeared on the right heel in 1942, and delay in healing necessitated her admission to hospital. This was the first of 14 admissions to various hospitals.

A diagnosis of pemphigus was made in 1946 when a blister developed on the right sole. Shortly after, a blister appeared over the dorsum of her left ring finger and the fingernail dropped off. The blister burst; the ulcerated area healed in the course of a month, but scarring resulted in clawing of the finger. At this time, examination revealed vulval ulcers.

Early in 1948, large painful ulcers on the right heel and left sole developed from clear blisters. Neurologic examination revealed blunting of pain sensation over the left hand and left foot, and the tendon reflexes were present and symmetric. Late in 1948, ulceration of the left heel and threatened gangrene of the toes of the right foot, which improved with bed rest, developed. On this occasion, the tendon reflexes in the arms were sluggish, knee jerks were brisk, and ankle jerks were absent, while the plantar responses were flexor. Light touch, pain, and temperature sensation were blunted over both lower limbs as high as the knees and over the dorsum of the left hand. Vibration sense was diminished in the legs. Roentgenograms of the feet were normal at that time.

In 1949, a deep ulcer exuding pus on the outer border of the left foot and a granulomatous mass at the base of the left little toe were noted. Radiograms of this foot showed destruction of the head of the fifth metatarsal and dislocation of this metatarsophalangeal joint. Amputation of the left little toe and distal three-quarters of the fifth metatarsal bone was performed. The diagnosis at this time was atypical syringomyelia.

Bilateral lumbar sympathectomy was performed in 1951, but no improvement resulted

and she continued to have recurrent blisters followed by ulceration of both feet and the left hand. The right hand was spared. In 1952, the right middle toe was amputated because the tip had become gangrenous. A diagnosis of dermatitis artefacta was made, and she received a course of electroconvulsive therapy.

In 1953, roentgenograms of the right foot showed subluxation of the terminal phalanges of the big and second toes, with areas of bone destruction in the tips of the terminal phalanges of these toes and in the proximal and middle phalanges of the fourth and fifth toes and complete disorganization of the proximal phalangeal joints of the latter toes.

In 1955, the right second and fourth toes were amputated and sequestra removed because the tips of the toes had become gangrenous, dropped off, and exposed bone. Histologic examination revealed "granulation tissue infiltrated by monocytes, polymorphs and many new capillaries. Bone scrapings show necrosis with loss of cement lines. The Haversian canals contain polymorphs and a few osteoclasts are present."

The tips of the fingers of the left hand dropped off in 1956, exposing bone, and the fingers were amputated at the proximal interphalangeal joints, except the little finger, which was totally amputated. Blisters appeared on the dorsum of the left hand late in 1956, and left cervical sympathectomy was performed. The right big toe was amputated because of bone necrosis. Corneal ulcers and an ulcer on the tongue developed, and it was thought on this occasion that the condition might be allied to myelodysplasia.

In 1958, an extensive blister appeared on the left leg, involving the lower third of the shin and the dorsum of the foot. This was grafted successfully. In the following weeks, she had a blister on the right buttock and it was discovered that she was insensitive to pinprick over both buttocks.

For four years, she has experienced a constant aching pain at the back of the neck, in the left upper and lower limbs and left side of the trunk, and, to a lesser extent, in the right thigh. She dislikes lying on her left side, and the left shoulder has stiffened. Walking has become progressively more difficult because her legs feel heavy and her balance is poor. She has never experienced paresthesias in her limbs. Although it was found on examination in 1948 that temperature and pain appreciation were depressed in her feet, she herself had not noticed any disability until about four years ago, when she found she was unable to determine the temperature of bath water with her feet or her left hand. The right hand has remained normal in appearance and perception.

During the past four years, she has noticed that her right forehead does not wrinkle and that the left side of her mouth appears to droop. Her eyes water excessively, and she has had recurrent red, painful eyes and ulcers on the left lower lid.

After an attack of herpes zoster of the right second cervical segment in 1945, the hair over the affected area fell out and has never regrown. Baldness gradually involved a similar area behind the left ear and the top of the scalp. After the shingles, she experienced slight deafness in the right ear, which has persisted. She has had no tinnitus.

Bowel habit and micturition have not been disturbed. At the age of 30, she married and has remained barren with irregular menses until her menopause at the age of 43. Her husband was interviewed and stated that he did not think his wife had deteriorated mentally nor did he think that the blisters could have been painful because she never complained of pain in them.

Her birth was illegitimate, but her parents are known and her family, which has been traced, contains no other affected member.

Examination. B.T. was of average build and looked older than her 57 years. She had hirsutes of the chin. Extensive vertical and bilateral postauricular alopecia was found (Fig. 1). The scalp in the bald areas was grossly scarred and showed infective eczematous lesions behind the ears. The skin was fixed over both pinnae, which were scarred, cracked, and bleeding in some places, and there was extension of this process into the external auditory meati. On the medial aspect of the right eyebrow was a small patch of folliculitis. Right nasal vestibulitis was present.

The skin over the face was mobile and of normal texture. The lanugo hairs were retained, and there was no diminution of sebum.

Fig. 1. Scalp of patient B.T., showing folliculitis decalvans

The right forehead was smooth and unfurrowed in contrast to the left, and she was unable to elevate the right eyebrow (Fig. 2A). Both upper eyelids were incapable of closure (Fig. 2B). The lower lip appeared to be drawn across to the left.

Lacrimation was profuse. Bilateral corneal opacities were noted, and the corneal surface was slightly ulcerated in some places. Left cervical and bilateral lumbar sympathectomy scars were present.

Trophic changes. The skin over the left hand, both feet, and left shin was scarred, dry, and atrophic but quite mobile. Ulcers were present on the left elbow, lower outer aspects of the right calf, and right instep. Each ulcer consisted of an area of granulation tissue about 1 in. in diameter. During her most recent admission, a clear, painless blister appeared overnight on the dorsum of the left thumb.

The right hand appeared normal. The multiple amputations can be seen in Figure 3.

Central nervous system examination. The patient was right handed. Speech was normal. Psychometric testing suggested that her initial intelligence was dull normal and that there had been mental deterioration. She had a high-stepping gait. Romberg's sign was positive.

Sense of smell was normal. Vision was 6/18 on the right and 6/9 on the left, both corrected; the visual fields were full and the fundi and disks normal. Pupils were equal and circular and reacted to light and accommodation. No nystagmus was noted, and external ocular movements were full apart from limited conjugate lateral gaze to the right. The palpebral fissures were wide, particularly on the left. Sensation over the face was normal, and corneal reflexes were brisk, although there was deficient eye closure. The jaw jerk was absent. She could not close either eye, particularly the right. She was unable to elevate the right eyebrow. Hearing in the right ear was defective, and an audiograph showed slight nerve deafness. Weber's test showed reference to the right. Palatal movement was good. The sternomastoids were strong, but there was some weakness of her left trapezius. The tongue was scarred.

No fasciculation or muscle wasting was found. Tone in the limbs was normal. Extension of the neck was limited. She was unable to elevate the left shoulder, which appeared "frozen." Slight diffuse weakness of both arms and marked weakness of the legs with bilateral foot drop were noted. Coordination tests were well performed in the arms, but there was considerable unsteadiness in the heel-knee test.

Supinator jerks were absent in both upper limbs, and biceps and triceps jerks were absent on the left and sluggish on the right. Only a right upper abdominal reflex was retained. Knee jerks were bilaterally brisk, and ankle jerks were absent. No plantar response was elicited. No sphincter disturbance was found.

Sensation. Vibration sense was absent in the left arm and below the waist. Position sense was normal. For light touch, pain, and temperature loss, see Figure 4.

General examination. The pulse was regular, and all peripheral pulses were palpable. The heart was not enlarged, and there were no cardiac murmurs. Upper dorsal scoliosis convex to the left was noted, but the lung fields were clear.

Fig. 2. Photographs of patient B.T. [A] Showi g inability to elevate right forehead. [B] Showing inability to close eyes

Fig. 3. Photographs of extremities

The alimentary system was normal. External genitals were normal. The vaginal introitus was narrow, and vaginal examination was unsatisfactory because the patient was distressed.

Investigation. Blood findings were hemoglobin 91%; white cell count 7,200 per cubic millimeter; platelets 180,000 per cubic millimeter; erythrocyte sedimentation rate 15 mm.

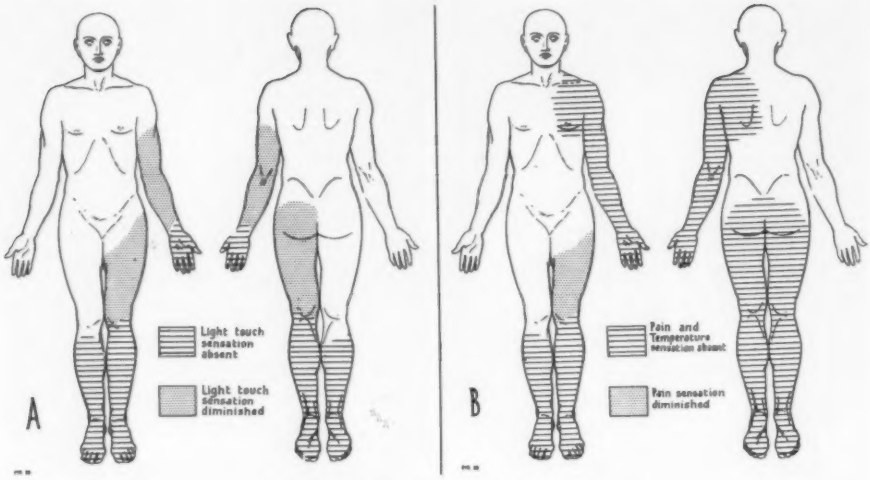

Fig. 4. Charts of sensory loss in B.T.

fall in one hour (Westergren); blood urea 37 mg. per 100 cc.; serum cholesterol 330 mg. per 100 cc.; and serum albumin/globulin 4.1 gm./2.7 gm. per 100 cc. Electrophoretic pattern showed a normal gamma globulin level. Liver function tests and serum calcium and phosphate were normal. The Wassermann reaction and Kahn test were negative.

Fig. 5. Roentgenograms of extremities

Cerebrospinal fluid. Lumbar puncture revealed a clear fluid under normal pressure, less than 5 cells per cubic millimeter, and 16 mg. of protein per 100 cc. Lange's test and the Wassermann reaction were negative.

Urinalysis disclosed no albuminuria or glycosuria. Microscopy was normal. A twenty-four-hour specimen contained no creatine but 920 mg. of creatinine.

An *electrocardiogram* was within normal limits. An *electroencephalogram* was normal. An *electromyogram* of right frontalis showed no electrical activity. *Roentgenograms* of the skull and chest were normal. The cervical spine had a normal sagittal diameter. Films of the hands and feet confirmed the loss of phalanges seen clinically; atrophic bony changes were seen in all phalanges and metatarsals, but the proximal ends of fingers 2, 3, and 4 of the left hand were intact. The right hand was normal (Fig. 5).

Biopsy findings. In July 1959, a muscle biopsy was taken from the left palmaris longus. A cutaneous nerve, which appeared gray and almost translucent, was taken at the same time.

"Osmic acid fixed preparations of this nerve showed that only one or two myelinated nerve

fibres in each nerve bundle remained (Fig. 6). Bielschowsky preparations showed that the axons were equally deficient, i.e. there was almost complete sensory denervation. Haematoxylin and eosin staining showed only a slight increase in the epi- and perineural connective tissue.

"The exposed muscle was small, but had a normal appearance with a well defined motor point. Haematoxylin and eosin staining showed groups of atrophic muscle fibres with some increase in the number of their sarcolemmal nuclei (Fig. 7). Cholinesterase preparations showed a reduction in the number of end plates of the subneural apparatuses, and those present showed a reduction in the number of their cups, which stained palely with a tendency to shrinkage. Vital staining with methylene blue showed a reduction in the number of subterminal nerve fibres and nerve fibres within the nerve bundles, those remaining in the latter showing an increased tendency to collateral branching (Fig. 8).

"A piece of skin, vitally stained with methylene blue, showed no sensory nerve endings or nerve fibres" (Dr. A. L. Woolf).

In October 1959, a piece of skin and muscle was removed from the right forehead. The amount of collagen tissue in the skin was diminished, consistent with senile degeneration. Hair follicles, sweat glands, and sebaceous glands were normal. Subcutaneous tissue was normal. No evidence of scleroderma was found. The piece of right frontalis muscle examined showed fibrous tissue containing striated muscle.

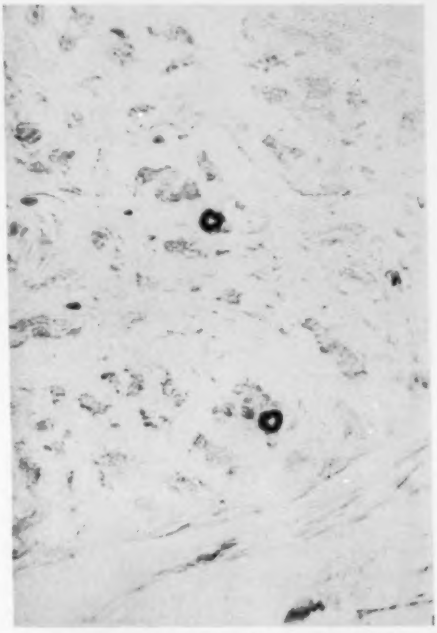

Fig. 6. Osmic acid–fixed preparations of a cutaneous nerve from the left forearm showing only 2 myelinated fibers. × 1,000

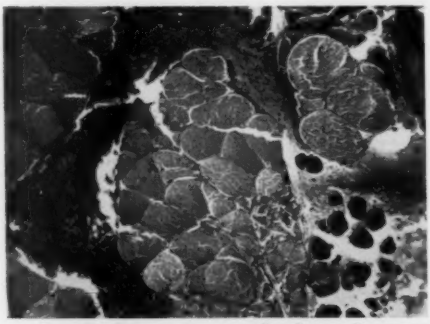

Fig. 7. From a section of palmaris longus muscle stained with hematoxylin and eosin, showing atrophic muscle fibers. × 240

DISCUSSION

While the term ulcerative mutilating acropathy is a descriptive one that could be applied to the end results of a number of conditions, such as leprosy and diabetes, it has acquired a special connotation since its use by Thévenard.[1] To draw an analogy from natural history, the term "trophic changes of the extremities" may be taken as a generic title and may be divided into various "subgenera" according to the underlying pathology, for example, leprosy. The term ulcerative mutilating acropathy should be reserved for a "subgenus," although, by definition, it could be argued as being the generic name.

Trophic changes of the extremities are found in such disorders as leprosy, tabes dorsalis, diabetes mellitus, and porphyria, which can all be confirmed by laboratory tests, and syringomyelia can be differentiated clinically without much difficulty. This paper will be confined to

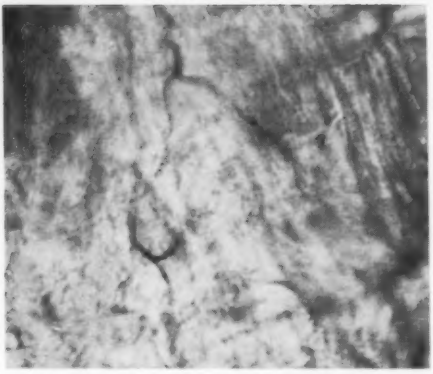

Fig. 8. From a section of palmaris longus muscle vitally stained with methylene blue. There is collateral branching of the few remaining axons in the intramuscular nerve bundles. × 800

a discussion of a group of conditions that may be called "radicular degenerations."

As was pointed out by Denny-Brown[15] and his associate England,[19] there is a close similarity between Charcot-Marie-Tooth amyotrophy and the disorder affecting the family described by Hicks,[12] which was shown by Denny-Brown to be a radicular sensory disorder. Indeed, in Charcot's original nonfamilial case, a severe peripheral sensory disorder was present and postmortem examination by Marinesco[20] revealed changes in the dorsal nerve roots and dorsal columns of the spinal cord. England and Denny-Brown described two patients with extensive sensory and trophic changes of radicular type in addition to the classical Charcot-Marie-Tooth syndrome. Van Bogaert's case[14] occupies an intermediate position between the Charcot-Marie-Tooth disorder and the sensory radicular neuropathy of Denny-Brown. Although there was no obvious muscular atrophy, at autopsy he found muscle lesions of neural type coexisting with the changes described by Denny-Brown affecting the peripheral nerves, dorsal roots, dorsal ganglia, and dorsal columns of the spinal cord.

Many reports of patients with skin ulceration, osteolysis, and dissociated sensory loss occurring singly or in combination can be found in the literature, but none of these are substantiated by biopsy or necropsy data. Particularly interesting in this respect are the cases of osteolysis without skin ulceration in which the bones of the fingers and toes become shortened and covered by loose, folded skin. This deformity has been called *main en lorgnette* because the appearance of the hands gives the impression that the fingers are pushed in like opera glasses.[21,22] *Main en lorgnette* has been reported in a case of advanced rheumatoid arthritis[23] and also in certain cases with endocrinopathies.[24] It may be assumed that many of these are variants of radicular degenerations, but, without more pathologic data, it is impossible to correlate the facets of the clinical picture with their causative neurologic lesions. They may be grouped together with the cases of Denny-Brown and van Bogaert pending further comprehensive clinicopathologic reports.

From both the clinical picture and the biopsy findings, the case of B.T. would appear to fall somewhere between the types described by Denny-Brown and van Bogaert, which were confirmed by autopsy. Changes in the peripheral nerves are common to all three cases. Muscle changes of lower motor neuron type are seen in van Bogaert's case and in B.T. Peripheral vascular changes are described only by van Bogaert.

Vascular lesions in the dorsal root ganglia consisting of amyloid degeneration of the small blood vessels are described by Denny-Brown and van Bogaert, and it is possible that such changes in the dorsal ganglia may exist in B.T. However, van Bogaert was able to demonstrate subendothelial and adventitious fibrosis with thickening of the walls of small vessels in the areas of osteolysis and ulceration, in the muscles at a distance from the ulceration, and even in the nerve root canal. He was of the opinion that these vascular changes were the result of a disturbance in neural control but that they probably aggravated the changes in the nerves they accompanied.

The sympathetic chains were not studied by Denny-Brown and van Bogaert in their otherwise comprehensive autopsy examinations. André and Goethals-Borin[25] reported a case of severe plantar perforations which were greatly improved by lumbar sympathectomy. In their

case, the first lumbar sympathetic ganglion was normal. The second ganglion appeared normal in its entirety, but, here and there, a few ganglion cells were surrounded by giant cells. The Schwann cords crossing the ganglia were thickened, and there was a dilatation of the small veins, chiefly at the poles of the ganglia. Bilateral lumbar and unilateral cervical sympathectomy in B.T. did not halt the development of new trophic lesions. Unfortunately, no histologic studies of the removed ganglia were made.

The case of B.T. shows some atypical features, the most remarkable being the complete sparing of the right upper limb despite the early involvement of the left hand, in which trophic changes have now progressed to gross deformity.

Thévenard,[17] in his review of 70 cases, found only 9 reported to have had all 4 limbs affected. In the majority of these, the trophic lesions of the upper limbs consisted of blisters and ulceration on fingers and hands, but Tocantins and Reimann[26] described 2 brothers with plantar perforations whose father had had phalangeal osteolysis resulting in the loss of several terminal phalanges and total amputation of 2 fingers. Eyckmans, Radermecker, and van Bogaert[27] reported the case of a patient with extensive necrosis of the 4 extremities at the age of 42 years. So far as I know, my case is the only one in which there is such gross trophic involvement of one upper limb. It was probably because of this that the disorder was considered psychiatric by many clinicians in different centers. B.T. was subjected to extensive psychiatric investigation and treatment over the years, and, when someone discovered that her birth was illegitimate, the psychiatric origin of her disability was considered to be established. The patient said that the accusation that she herself was responsible for these recurrent digital ulcerations caused her more anguish over the years than the actual disability.

It is noteworthy that not until 1956—after nineteen years of progressive disability, repeated hospital investigations, psychiatric treatment, and 2 sympathectomies—was she referred to a neurologist.

Subjective sensory disorders were recorded in the family described by Hicks and consisted of lightning pains affecting first the lower limbs, then any part of the body, and occurring months or years after the appearance of ulcers. Similar pains have not been reported by other writers. The pain experienced by B.T. was of a dull, aching character affecting predominantly the left side of the body. She was unwilling to lie on this side because of the unpleasant sensation she experienced, and this raised in our minds the possibility of a thalamic disorder.

Objective sensory disorders were a constant feature in the 70 cases reviewed by Thévenard. He was of the opinion that they probably constituted the first sign of illness, but this could only be appreciated retrospectively. The sensory loss followed the distal distribution of the acropathy, often extending to mid-thigh, in a few cases to the groin, and in 3 cases to the xiphisternum. It was usually symmetric even if ulcers affected only one foot. Thévenard noted that the sensory disturbance in the upper limbs had been recorded more frequently since 1942 and that the spread in the upper limbs was the same as that in the legs. In 3 cases, sensory loss reached the root of the upper limb. Neither anogenital nor suspended sensory loss on the trunk had been reported.

Thévenard[17] divided the 70 cases reviewed fairly equally into 3 groups according to the loss of light touch, pain, and temperature over the affected areas:

- Group 1: equal loss of the 3 modalities
- Group 2: syringomyelic dissociation
- Group 3: loss of 3 modalities distally and syringomyelic dissociation in the proximal segment.

Denny-Brown concluded that sensory dissociation was prominent in this disease because it was primarily a radicular affection and the degree of dissociation became less as more nerve roots were affected.

The sensory disturbance in B.T. can be included in Group 3 as described by Thévenard. The striking absence of sensory loss in the right upper limb, the extension of syringomyelic sensory loss over the left side of the chest, and the absence of vibration sense as high as the waist and in the left arm are more unusual features. Position sense was normal. The reflex pattern was fairly typical of other cases in the literature.

Deafness was a feature of the disease in the family described by Hicks and in one case described by van Bogaert. B.T. had defective hearing in the right ear after an attack of herpes zoster. Another sequel of this illness was a lopecia of the right side of the scalp. A dermatologist was consulted and was of the opinion that the gross cicatricial alopecia was the result of folliculitis decalvans. This condition is essentially a folliculitis leading to death of hair follicles and the elastic and connective tissue between them. No association between folliculitis decalvans and ulcerative mutilating acropathy has been reported.

Several puzzling features remain in the case of B.T. Eye closure was deficient bilaterally, and there was immobility of the right forehead with electromyographic evidence of absent electrical activity in the right frontalis muscle. The biopsy taken from this muscle showed fibrous tissue containing striated muscle but was too small to enable any definite conclusion to be drawn. Weakness of the left trapezius was noted but no wasting, and electromyography of the left shoulder girdle was not performed because the patient was unwilling. Another finding that could not be explained was the presence of profuse lachrymation. Salivation was not disturbed and sweating over the face was normal. The occurrence of corneal, oral, and vulval ulcers in B.T. raised the possibility of Behçet's syndrome, but studies on blood and cerebrospinal fluid have proved negative.

SUMMARY

A sporadic case of ulcerative mutilating acropathy with certain unusual features is described.

Biopsy studies of nerve and muscle suggest that the underlying pathology is probably degeneration of dorsal root ganglia.

The literature is reviewed.

The author thanks Dr. A. L. Woolf for performing and reporting the biopsy studies and Dr. J. D. Spillane for advice and permission to publish this case. The sensory charts were prepared by the late Ernest Stilling.

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Pathogenesis of cerebral vasospasm in hypertensive encephalopathy

I. Effects of acute increases in intraluminal blood pressure on pial blood flow

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DURING THE COURSE of malignant hypertension, sudden rises of diastolic blood pressure are often accompanied by transient signs and symptoms generally called "hypertensive encephalopathy."[1-4] Symptoms such as headache, drowsiness, nausea, vomiting, scotomas, and mental obtundity are common. Neurologic signs regularly include focal or generalized seizures, papilledema, retinal edema, spasm of the retinal arterioles with hemorrhages, transient hemiparesis or monoparesis, and defects of the visual fields. During such periods of severe hypertension, intracerebral hemorrhage[5] or rupture of intracranial arterial aneurysms or malformations may occur. Cerebrospinal fluid pressure is usually increased during these hypertensive crises. The signs and symptoms may be rapidly alleviated by careful reduction of the arterial blood pressure to near normal.

It has been our experience that, occasionally, patients with atherosclerotic stenosis or occlusion of a major cerebral artery (in whom the diagnosis had been confirmed by arteriograms) have circulatory insufficiency in the territory supplied by the diseased vessel during episodes of severe hypertension (elevation of the diastolic blood pressure above 120 mm. Hg). We have found that cautious reduction of the blood pressure in such patients by means of hypotensive drugs may result in improvement in the focal cerebral symptoms provided the systolic blood pressure is not reduced below approximately 180 mm. Hg; reduction below this level may produce a hemodynamic crisis with infarction due to hypotension. On the basis of clinical observations, therefore, it would appear that, at both ends of the scale of blood pressure (excessively high or excessively low levels), symptoms of ischemia may appear in the territory of supply of an occluded or stenotic artery because of failure of the collateral circulation. The explanation of the production of symptoms by a severe fall in blood pressure with failure of the collateral blood flow is now well established,[2,3] but the rare production of symptoms by an excessive rise in blood pressure has been difficult for us to understand.

This and a later communication[6] will report a series of experiments designed to clarify any "vasospasm" that might be present in the cerebral vessels during severe hypertension since such spasm is often seen in the retinal arterioles in the course of hypertensive encephalopathy.

REVIEW OF LITERATURE

Before we describe the present series of experiments, important observations made by earlier investigators will be summarized because they indicate mechanisms that may be responsible for hypertensive cerebral crises.

In 1876, Gowers[7] commented that, in

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Bright's disease, the retinal arteries as seen with the ophthalmoscope were visibly narrowed by contraction and that the contraction, as a rule, was in direct proportion to the blood pressure. He favored the view that the increased blood pressure in Bright's disease was due to contraction of the minute arteries and probably not vice versa. In 1902, Bayliss[8] concluded from his experiments that the muscular coat of arteries, like smooth muscle in other parts of the body, reacts to a stretching force by contraction.

Kety and associates[9] showed by direct measurements in man that essential hypertension is associated with a marked increase in cerebrovascular resistance, averaging 88%, which appeared to correlate with the grade of retinopathy. Hafkenschiel, Friedland, and Zintel[10] found that reduction of the blood pressure in such hypertensive patients by subtotal adrenalectomy lowered the cerebrovascular resistance toward normal. Fog[11] reported that, in the cat, a rise in intravascular pressure caused contraction of the pial arteries. In his experiments, the rise in blood pressure was caused by intravenous injection of epinephrine, stimulation of splanchnic nerves, and, in a few experiments, compression of the abdominal aorta.

In 1954, Byrom[1] performed a carefully planned study of experimental hypertensive encephalopathy in the rat. Hypertension was produced by means of a Goldblatt clamp placed on one renal artery, and the pial vessels were observed and photographed through a cranial window. Cerebral symptoms never occurred until the systolic blood pressure exceeded 200 mm. Hg, and the symptoms were promptly relieved when the hypertension was abolished by removal of the Goldblatt clamp. Photographic records of the pial vessels during hypertensive encephalopathy showed pallor, arterial narrowing, or spasm occurring either diffusely or in small segments. Byrom mentioned 3 possible causes of cerebral arterial spasm in severe renal hypertension: [1] excessive vasoconstriction as a response to increased intraluminal pressure; [2] the effect of a circulatory vasoconstrictor factor; and [3] abnormal irritability of the arteries in response to normal blood pressure. Histologically, the brains of these animals showed focal arterial necrosis, miliary infarcts, and hemorrhages.

EXPERIMENTAL DESIGN

The purpose of the experiments reported here has been to determine whether an acute increase in intraarterial luminal pressure uncomplicated by any circulating pharmacologic agent is capable of producing cerebral vasospasm. In all experiments, one carotid artery was ligated in order to compare the effects of acute and chronic hypertension on the vessels of a normal and an ischemic area. In a forthcoming communication, experiments to clarify the nature of cerebral vasospasm in experimental renal hypertension, using the technics of Goldblatt[12] and Page,[13] will be discussed.

MATERIAL AND METHODS

Experiments were performed on 17 Macacus rhesus monkeys and 18 cats. They were divided for convenience into acute and chronic groups. The acute experiments were performed on 13 cats and 3 monkeys and will be described in this communication. The results of the chronic experiments, in which renal hypertension was induced, will be reported separately[14]; 3 of the chronic animals were also used for observation of the effects of hypertension induced by epinephrine prior to the induction of hypertension by renal ischemia.

All acute experiments were performed after induction of light intravenous Nembutal anesthesia with average doses of 30 mg. per kilogram of body weight and 0.5 mg. of atropine. A tracheostomy was performed, a tracheal cannula was inserted, and constant artificial respiration was maintained with a Harvard respirator at constant respiratory exchange. The head was fixed in position with an adjustable head-holder (Baltimore Instrument Co.). A polyethylene catheter was inserted into the proximal end of the right carotid artery and connected to a Statham arterial pressure transducer (Model P23AA, Statham Instruments, Inc., Hato Rey, Puerto Rico) for recording blood pressure. The distal segment of the right carotid artery was ligated or clamped with a small Crutchfield arterial clamp (American Instrument Co., Silver Springs, Md., Figure 1A). A compensator was connected to the pressure dome of the transducer so that a solution of heparinized saline could be injected through the system into the artery at a constant rate of 2.1 cc. per hour. In this manner,

clotting within the recording system was prevented and the arterial pressure could be recorded for as long as eight hours without artefact due to blood clot. A polyethylene catheter was also placed in the femoral vein for those experiments on the effect of hypertension induced by epinephrine or hypertensin.

A transverse incision was made over the fifth or sixth costal interspace on the left, the ribs were separated, and the aorta was exposed. A Salibi or Crutchfield arterial clamp (V. Mueller Co., Chicago) (Fig. 1A) was then placed loosely around the descending thoracic aorta, with the handle for tightening the clamp protruding from the wound.[15] The ribs were sutured together with wire and the skin and subcutaneous tissue closed around the clamp handle with silk sutures. In this manner, the aortic clamp could be closed by turning of the handle protruding from the closed wound and acute mechanical hypertension confined to the circulation of the brain and the upper extremities could be induced at will. The elevation of blood pressure could also be promptly terminated by opening of the clamp. In this manner, repeated elevations of blood pressure of various durations could be induced in the same animal. In 4 monkeys and 5 cats, an attempt was made to produce chronic hypertension within the cerebral circulation by partial closing of the aortic clamp. We were unable to achieve this because prolonged elevation of the intracranial blood pressure resulted in death within thirty-two hours.

In many experiments, the intracranial or cerebrospinal fluid pressures were recorded by means of a sensitive Statham pressure transducer (Model P 23B, Statham Instrument Co., Hato Rey, Puerto Rico). A No. 18-gauge needle was inserted into the cisterna magna for recording the cerebrospinal fluid pressure; occasionally, intracranial pressure was recorded directly from a hole machined into the skull windows. The windows were screwed into the calvarium over both the intact and the ischemic hemisphere. The skull windows were modified after those designed by Forbes and were machined out of stainless steel and glass. Immediately anterior to the window, a hole through the skull was made with a twist-drill, the dura was opened, a thermistor was inserted into the cortex, and the skull was sealed

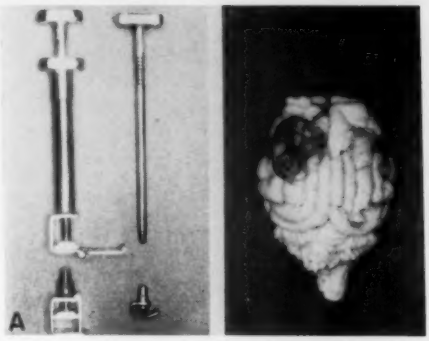

Fig. 1. [A] Types of clamps used in these experiments. Larger clamp on left is Salibi type, which is separated from the handle for closing the clamp below and attached for tightening above. Small clamp to right is Crutchfield model. [B] Brain removed from a cat in which acute cerebrovascular hypertension had been produced repeatedly by clamping of thoracic aorta. Bilateral skull windows were removed after right carotid artery had been ligated. Note that herniation of brain from swelling is limited to left hemisphere with intact carotid circulation.

around the thermistor with plastic cement. The thermistor was inserted in order to record relative changes in the pial blood flow.[3] The blood pressure, intracranial or cerebrospinal fluid pressure, and pial blood flow were concurrently recorded with an Offner Type D electroencephalograph.

The pial circulation of both the normal and the ischemic hemisphere was observed and repeatedly photographed through a macrophotography system consisting of 2 35-mm. Praktina single-lens reflex cameras, a long extension tube with bellows, a rack and pinion focusing device, and a single photographic lens consisting of a Zeiss Tessar 50-mm. lens or a Zeiss Flektagon 35-mm. lens. These gave magnifications of × 56 and × 80 on an 8 x 10 in. print. Illumination was by stroboscopic electronic flash units firing on the brain.

In 1 animal, a three-way stopcock attached to a wide syringe containing 30 cc. of warm, heparinized blood was inserted between the divided ends of the common carotid artery so that, by turning the stopcock, blood that was under measured pressures could be injected into the distal end of the vessels. The femoral

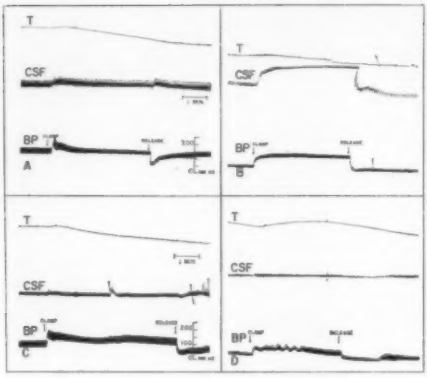

Fig. 2. Samples of records made in different experiments in the cat, showing effects of acute cerebrovascular hypertension induced by clamping of thoracic aorta on carotid blood pressure (BP), cisternal cerebrospinal fluid pressure (CSF), and cortical blood flow (T). [A] Skull closed. Arrow indicates closure of aortic clamp. Blood pressure rises from 175/130 to 245/175. Cerebrospinal fluid pressure rises and falls are comparable to changes in blood pressure. Cortical flow shows transient increase followed by marked decrease (vasoconstriction). When clamp is released, blood pressure returns to 150/110 after transient fall to 75/50. Cerebrospinal fluid pressure rises during fall in blood pressure (vasodilation), and cortical flow increases (vasodilation). [B] Skull intact. After loss of blood ,initial blood pressure is 65/50; clamping of aorta raises pressure to 145/105, resulting in increase in cerebrospinal fluid pressure and decrease in cortical flow. Pattern is comparable to A, but decrease in cortical flow is less striking. [C] Skull and dura removed. Initial blood pressure is 110/75; when clamp is closed, pressure rises to 190/140 with decrease in cortical flow comparable to that seen in A. [D] Skull removed. Blood pressure at shock levels after blood loss. Clamping of aorta raises pressure from 50/25 to 100/75 with increase in cortical flow.

blood pressure was also recorded continuously with the carotid blood pressure. When the stopcock was opened and the syringe manually compressed, the intraluminal pressure of the cerebral vessels could thus be manipulated independently from the systemic blood pressure.

In 1 cat, the base of the brain was elevated with self-retaining retractors and the circle of Willis, the middle cerebral artery, and its major branches were photographed before and after induction of hypertension by clamping of the aorta in order to compare any effects of changes in intraluminal pressure on the large vessels at the base as well as on the convexity. In this same animal, the lateral ventricle was opened by removal of brain by suction and the main choroidal vessels supplying the lateral ventricle were also photographed before and after the induction of hypertension.

In 3 additional monkeys, the effects of the intravenous injection of 0.25 to 0.5 cc. of 1:1,000 epinephrine were photographed.

In 1 monkey, the effects of repeated long intravenous injections of purified hypertensin* (angiotensin or angiotonin) on the vessels, pial blood flow, cortical oxygen tension (recorded polarographically), *p*H, and PCO_2 were recorded.

RESULTS

Production of acute cerebrovascular hypertension by clamping the aorta. The method of producing a sudden sustained rise in the intraluminal pressure of the cerebral arterial system by rapidly tightening the clamp placed around the thoracic aorta below the origin of the innominate, subclavian, and carotid arteries was found to be most satisfactory. This produced an immediate rise in blood pressure, both systolic and diastolic, of 75 to 100% in either the cat or the monkey, and, occasionally, the systolic blood pressure reached levels as high as 245 mm. Hg. The effects on the cerebral circulation were essentially the same in the cat as in the monkey.

Changes in cerebrospinal fluid pressure and vascular caliber. The cerebrospinal fluid or intracranial pressure showed an immediate increase proportional to the rise in blood pressure and showed a response expected of a plethysmograph (Fig. 2A and B). Pial veins usually showed some passive distention, which persisted, but the pial arterioles of 35 to 1,000 μ internal diameter showed rapid transient vasodilation followed within thirty to forty-five seconds by a diffuse, progressive constriction over the next five minutes, which might amount to a reduction in caliber of as much

*Hypertensin-Ciba was kindly made available by Ciba Pharmaceutical Products, Inc., Summit, N. J. The decapeptide angiotensin is produced by the action of renin on its substrate; this is subsequently transformed to the vasoconstrictor octapeptide angiotensin II (hypertensin) by a chloride-activated enzyme of the plasma.

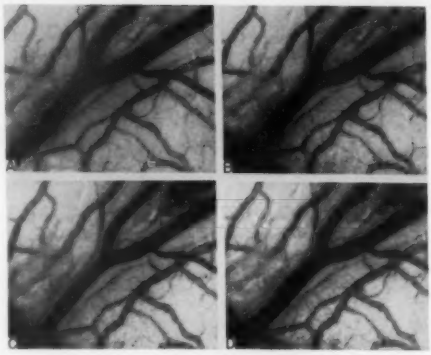

Fig. 3. Serial pictures (x 50) of the same area of pial circulation of a cat before, during, and after the induction of hypertension by clamping of thoracic aorta. Skull was intact, and photographs were made through skull windows. Main trunk of arteriole in center of field in A measures 150 μ. [A] Blood pressure of 120/80. [B] Thirty seconds after clamping, pressure is 165/110, arteriole shows moderate constriction, cerebrospinal fluid pressure is increased, and cortical flow is decreased. [C] Three hundred forty seconds after clamping, pressure is 165/100, arteriole is markedly constricted, cerebrospinal fluid pressure remains elevated, and cortical flow is reduced. [D] Sixty seconds after release, pressure is 105/60, cerebrospinal fluid pressure is further increased, and cortical flow is less reduced.

as 50% (Figs. 3, 4, and 9). The maximal reduction in caliber occurred in vessels of 40 to 250 μ in size. The larger cerebral vessels, such as the internal carotid and main trunk of the middle cerebral artery (2 mm. and more), showed little change in caliber during sudden intraluminal hypertension, but the secondary and tertiary branches (1 mm. and less) showed marked constriction (Fig. 9). The choroidal vessels supplying the lateral ventricles showed a response similar to that of the pial vessels, as seen in 1 experiment. Arteriolar spasm similar to that seen in severe renal hypertension[1,14] was not produced by hypertension resulting from clamping of the aorta.

The possibility that the constriction of the pial arteries might be due to brain swelling, which invariably accompanied the increase in intraluminal pressure, was considered. In sudden increase of intracranial pressure, collapse of cerebral vessels due to compression was described by Cushing in his classic experimental study published in 1902.[16] This possibility was excluded as the cause of the arteriolar constriction because it occurred when the blood pressure was raised with the skull windows in place or removed and the brain was permitted to herniate (Figs. 7 and 8) or when the entire calvarium was removed (Fig. 9). It was of special interest that the brain herniated through the skull opening on the side of the intact carotid artery but did not do so on the side of the occluded carotid artery (Fig. 1B). However, the pial vessels appeared to show as much constriction in the distribution of the occluded carotid artery as over the intact hemisphere.

After repeated application of the aortic clamp or after prolonged induction of hypertension by this method, severe brain swelling did occur and the brain vessels became compressed against the window, resulting in the spurious appearance of "vasospasm" during the induction of hypertension (Fig. 5C and D). This could be demonstrated to be due to brain swelling and compression because the vessels assumed a normal appearance after removal

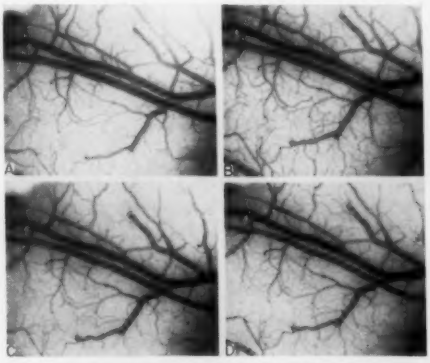

Fig. 4. Serial pictures (x 25) of pial circulation of cat before, during, and after induction of severe hypertension by clamping of thoracic aorta. Artery with light reflex running transversely across field in A measures 100 μ. Skull is intact; photographs were taken through skull window. [A] Blood pressure is 110/80. [B] Ten seconds after clamping, pressure is 250/200 and artery is transiently dilated with distention of veins. [C] Thirty seconds after clamping, pressure is 200/170 and arteriole is constricted. [D] One hundred seconds after clamping, pressure is 180/155 and arteriole is further constricted.

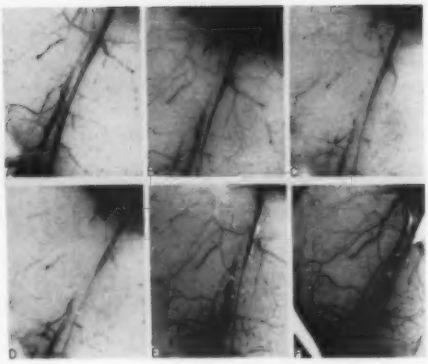

Fig. 5. "Artifactual spasm" produced by brain swelling with progressive compression against skull window during experimental hypertension (Cushing effect). Serial photographs (× 30) of pial circulation of cat before and after repeated bouts of hypertension produced by clamping of thoracic aorta. Arteriole running vertically across field measures 100 μ. [A] After release of first aortic clamping, blood pressure is 70/20 and brain is swollen and compressed against skull window. [B] Nine hundred seventy seconds after second clamping, pressure is 160/100 and artery is compressed against window, giving impression of spasm. [C] Twenty seconds after third clamping, pressure is 160/50 and artery and veins are further compressed. [D] Thirty seconds after release, pressure is 50/20, arteriole has appearance of "segmental spasm" due to compression, and veins and capillary bed are bloodless. [E] Window removed. Pressure is 60/20 and vessels are beginning to refill as compression is relieved. [F] Seven hundred seventy seconds after fourth clamping, with window removed. Pressure is 130/60, and artifactual spasm due to compression is relieved.

of the windows with decompression (Fig. 5E and F).

Production of perivascular cerebral hemorrhages by acute intraluminal hypertension. Occasionally, the rapid induction of severe hypertension, that is, a blood pressure of 220/160, resulted in the appearance of periarteriolar and pericapillary ball-shaped and linear hemorrhages and rarely in subarachnoid hemorrhages (Fig. 6). However, the intravenous injection of trypan blue showed little if any evidence of damage to the blood-brain barrier except at hemorrhage sites. Segmental arteriolar spasm was never seen consequent to simple increase of intraluminal arteriolar pressure.

Pial blood flow in hypertension. Records of pial blood flow made with a thermistor showed that the diffuse arteriolar constriction accompanying the increase in intraluminal pressure is also accompanied by a significant reduction in cerebral blood flow provided the initial systolic blood pressure is not below 60 mm. (Fig. 2A, B, and C); if the initial blood pressure is below 60 mm., raising of the blood pressure by application of the aortic clamp then results in increased pial blood flow (T). Photographs of the pial arterioles during such experiments show that, when the systolic blood pressure falls below 60 mm. Hg, the intraluminal pressure is insufficient to maintain the vascular tone and arteries tend to collapse and constrict. When pressure is raised after such a state, the vessels dilate rather than constrict.

Close examination of concurrent records of carotid blood pressure, intracranial pressure, and pial blood flow (T) and serial photographs of pial vessels shows that, after a sudden rise in intraluminal pressure, the first occurrence is a passive distention of pial arteries for ten to forty-five seconds accompanied by

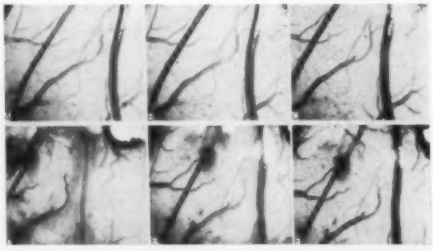

Fig. 6. Production of periarteriolar and pericapillary hemorrhages by repeated bouts of severe hypertension. Serial photographs (× 35) of pial circulation of cat; larger arteriole to right of field measures 80 μ. [A] After several clampings of aorta with release, blood pressure is 140/110 and small pericapillary hemorrhages are seen in left corner of field. [B] Ten seconds after another clamping, pressures is 220/160. [C] Two hundred ninety seconds after clamping, pressure is 190/140 and pericapillary hemorrhages are increasing. [D] Seven hundred twenty seconds after clamping, pressure is 180/150 and numerous ball and flame hemorrhages are seen. [E] Twenty seconds after release, pressure is 90/80. [F] Two hundred ten seconds after release, pressure is 110/80 and hemorrhages are clearly visible. Brain is also severely swollen (windows removed).

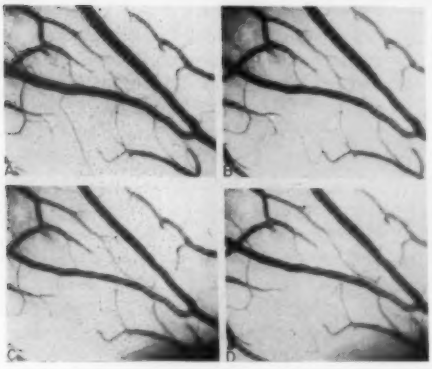

Fig. 7. Serial photographs of pial circulation of cat seen in Figure 8, showing comparable effects of acute hypertension with skull windows in or out. In this series, windows are in place. Cerebrospinal fluid, cortical blood flow, and blood pressure were concurrently recorded. [A] Control record; blood pressure is 120/100, and large pial arteriole measures 136 μ. [B] Forty seconds after clamping of aorta, pressure is 180/140, pial arteriole measures 140 μ, cerebrospinal fluid pressure is increased, and pial flow is beginning to decrease. [C] Three hundred sixty seconds after clamping, pressure is 180/145, cerebrospinal fluid pressure is increased, pial flow is markedly decreased, arteriole measures 112 μ, and perivascular hemorrhages appear. [D] Sixty seconds after release, pressure is 130/90, cerebrospinal fluid pressure is normal, and pial flow is improved.

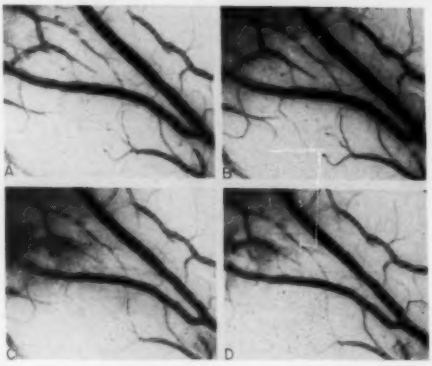

Fig. 8. Serial photographs of pial circulation of cat seen in Figure 7. Skull windows and subarachnoid hemorrhages have been removed. [A] Blood pressure is 110/70, and pial arteriole measures 136 μ. [B] Forty seconds after aorta is clamped, pressure is 160/130, cerebrospinal fluid pressure is unchanged (decompression), pial flow is decreased, and arteriole measures 108 μ. [C] One hundred ninety seconds after clamping, pressure is 150/125, cerebrospinal fluid pressure is unchanged (decompression), pial flow is markedly reduced, and pial arteriole measures 78 μ. [D] Forty seconds after release, pressure is 110/70, cerebrospinal fluid pressure is unchanged (decompression), pial flow is improved, and pial arteriole measures 118 μ. Figures 7 and 8 show that hypertensive arteriolar constriction of cerebral vessels is not due to compression by brain swelling.

a transient rise in pial blood flow (T) and cerebrospinal fluid pressure. Thereafter, there is progressive reduction in the caliber of small pial arteries, in pial blood flow (T), and in cerebrospinal fluid pressure. When the blood pressure is lowered by unclamping the aorta, pial arterioles dilate, cortical blood flow increases, and cerebrospinal fluid pressure rises, despite a fall in blood pressure, due to vasodilation.

Brain swelling, vascular compression, and medullary ischemia in hypertension. Rarely, when repeated elevation of the blood pressure caused marked brain swelling, the following sequence of events took place. With the rise in blood pressure, the pial arterioles constricted, the brain became progressively swollen, the cerebrospinal fluid pressure steadily rose, and the pial blood flow decreased. Ultimately, the swollen brain compressed the vessels against the skull window; then, a further rise in blood pressure occurred, apparently because of ischemia of the vasomotor center resulting from increased intracranial pressure (Cushing effect). This produced a vicious circle resulting in death from brain herniation. None of the animals in which the aortic clamp had been closed survived for longer than eight to thirty-two hours, dying with dilated pupils and respiratory failure; at necropsy, swelling of the brain was found.

Although it was possible to demonstrate photographically that the pial vessels constrict during severe hypertension whether the skull is open or closed, the reduction of pial blood flow recorded by the thermistor during hypertension was so remarkable that several experiments were devoted to proving that mechanical factors, such as pressure of the swollen brain against the thermistor in the closed skull, were

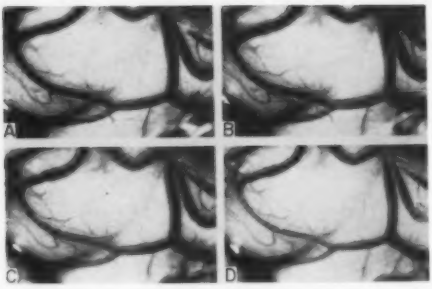

Fig. 9. Low power pictures (× 5) of main branches of middle cerebral artery of cat before and after induction of hypertension, showing that constriction is limited to secondary and tertiary branches of 1,000 μ and less. Main trunk of middle cerebral artery is in right lower corner; smaller branches are to left of field. [A] Before aortic clamp is applied, blood pressure is 100/50. [B] Eight seconds after clamping, pressure is 160/120. [C] One hundred twenty seconds after clamping, pressure is 155/120, smaller branches of middle cerebral are constricted, and major branches are unchanged. [D] Eight seconds after release, pressure is 70/30 and constriction of small branches only is still present.

not the cause of the decreased blood flow. However, comparable decreases in pial blood flow were recorded with or without a wide bilateral craniectomy. In those experiments in which the thermistor was resting lightly on the exposed brain, careful inspection through the magnifying system of the camera showed that compression of the vessel did not occur.

Incidental observations. When the clamp was placed on the aorta, a depressor reflex commonly resulted, presumably as a result of pressure receptors in the aortic arch. Repeated episodes of acute hypertension resulted in aggregation of erythrocytes and slowed blood flow in the pial circulation immediately after the clamp was released, in spite of a maintained blood pressure of 100 mm. or more. The reason for this sudden and transient impaired flow in small vessels after sudden restoration of blood pressure from hypertensive to normal levels was not clear but appeared to depend in part on the following factors: brain swelling with increased vascular resistance due to compression, localized hemoconcentration, and vascular damage.

Effects of mechanical injection of blood into the carotid artery under pressure. The results of injecton of blood into one carotid artery under measured pressure produced arteriolar constriction comparable to that reported above, but the experiments were technically less satisfactory for several reasons: air embolization occurred, only the systolic pressure was increased, and donor blood mixed with heparin and saline were injected.

Effects of intravenous epinephrine injection. Increase in blood pressure produced by the intravenous injection of 0.25 to 0.5 cc. of 1:1,000 epinephrine resulted in changes comparable to those reported by Fog.[11] In most animals, pial arteriolar constriction occurred during the hypertensive phase. However, this method of inducing change in intraluminal pressure is less satisfactory than the use of the aortic clamp because epinephrine has a transient and possibly direct pharmacologic effect on the smooth muscle wall of pial vessels.

Effect of intravenous injection of ischemic renal blood on pial vessels. In 3 cats, the effect of an intravenous transfusion of 15 to 25 cc. of ischemic renal blood from a donor animal was studied because such blood is rich in renin, the precursor of the circulatory vasoconstrictor factor in renal hypertension.[17,18] Records of the blood pressure, intracranial pressure, and pial blood flow and photographs of the pial vessels were made; 1 experiment was considered unsatisfactory because the initial blood pressure was low due to blood loss before the injection of the ischemic renal blood. In the 2 successful experiments, there was a small rise of 20 to 25 mm. in the blood pressure after a delay of three minutes with slight (20%) constriction of the pial arterioles. No significant changes in pial blood flow or cerebrospinal fluid pressure were noted.

Effect of intravenous injection of hypertensin on cerebral blood flow and metabolism. Repeated intravenous injections of 1 mg. of hypertensin resulted in a highly reproducible sequence of events. Blood pressure rose from normotensive to hypertensive levels (175 to 220 mm.). Intense pial arteriolar constriction greater than 50% was noted and persisted for several minutes after the blood pressure had returned to normal levels. The brain became visibly tense and swollen. The pial blood flow (T) and cortical oxygen tension were reduced.

The brain PCO_2 and *p*H were usually moderately reduced. The cerebral arteriolar constriction and decreased cerebral blood flow were far more marked than any changes observed after the injection of epinephrine.

DISCUSSION

Simple mechanical increase in the intraluminal arterial tension of cerebral vessels from normotensive to hypertensive levels causes brain swelling and constriction of cerebral arterioles of 35 to 1,000 μ in size, resulting in decreased cerebral blood flow and increased intracranial pressure. Constriction of arterioles was never as great as that seen in the arteriolar spasm of experimental renal hypertension. Pericapillary and periarteriolar hemorrhages rarely result, but brain swelling may be so severe that cerebral vessels are compressed to the point of stenosis or occlusion, reducing further an already impaired cerebral blood flow. Furthermore, if severe hypertension continues, brain swelling may result in cerebral herniation with ischemia of the vasomotor center and a further rise in blood pressure, thus establishing a vicious cycle ultimately leading to death. For this reason, none of our animals in which the descending aorta was clamped survived for longer than thirty-two hours, and, at autopsy, gross swelling of the brain was evident.

Since acute hypertension was induced by mechanical means, resulting cerebral vasoconstriction was not due to any circulating factor. Although brain swelling regularly accompanied cerebrovascular hypertension, it was not responsible for the immediate arterial constriction by vascular compression. Since the animals were undergoing constant artificial respiration, changes in arterial oxygen and carbon dioxide levels of the blood were not responsible for changes in vascular caliber. It therefore seems established that constriction of small cerebral vessels with reduced blood flow is a physiologic response to a rapid increase in intraluminal blood pressure, but this response alone does not cause the degree of arteriolar constriction seen in severe renal hypertension with arterial spasm.

In the cat and monkey, occlusion of one carotid artery protects the hemisphere supplied by that vessel from brain swelling during acute hypertension but the pial arterioles over the ischemic hemisphere show constriction comparable to that seen over the intact hemisphere. Brain swelling regularly results when the blood pressure exceeds 180 mm. and is predictable because the filtration pressure greatly exceeds the colloid-osmotic pressure, with consequent loss of plasma fluid into the brain.[3] Occlusion of the carotid artery protects the ischemic hemisphere from this effect. When the systolic blood pressure exceeds 180 mm., a progressive tonic contraction of the smooth muscle of the small arteries throughout the brain occurs, but there is little or no change in the caliber of the large arteries of the circle of Willis. Occlusion of the carotid artery does not protect the meningeal arterioles from vasoconstriction because the rich arteriolar anastomoses of the pia permit diffuse dissemination of changes in intraluminal pressure over the pial vascular bed.

This remarkable dependency of the pial vessels on changes in intravascular pressure, the Bayliss effect, has been noted in earlier studies in which the vascular intraluminal pressure was lowered during hypotension or as a result of vascular occlusion.[3,8] The fall in intraluminal pressure in an area of ischemia results in vasodilation with a compensatory increase in blood flow in the ischemic area. Since severe hypertension causes vasoconstriction of the collateral vessels, this compensatory collateral circulation tends to be impaired.

Segmental spasm of the arterioles such as Byrom reported in renal hypertension was not seen in any of these experiments in which acute mechanical cerebrovascular hypertension was induced, and we do not consider this physiologic vasoconstriction of sufficient degree to warrant the term "vasospasm." This term should be reserved for a different pathologic entity seen in severe renal hypertension with a reduction of arterial caliber by over 50%, which will be described in a later communication. In the experiments in which the effects of intravenous infusion of ischemic renal blood rich in renin was studied, there was only slight pial arterial constriction.

A transient but more marked degree of pial arteriolar constriction was regularly seen after intravenous injection of hypertensin, the circulatory vasoconstrictor substance known to be

present with renal hypertension. This intense cerebral arteriolar constriction is far greater than any ever seen after intravenous injection of epinephrine and is accompanied by marked reduction of blood flow, cerebral anoxia, and some accumulation of acid metabolites in the brain. The arteriolar constriction persists after the blood pressure has returned to normal levels. Therefore, it appears probable that hypertensin or other circulatory factors may render the pial vessels excessively sensitive to intraluminal pressure changes. Evidence showing that this sequence takes place in chronic hypertension will be reported later.

CONCLUSIONS

1. Acute mechanical increase in cerebrovascular intraluminal pressure induced by clamping of the thoracic aorta distal to the origin of the cerebral vessels results in constriction of small cerebral arteries measuring 35 to 1,000 μ in internal diameter. The large vessels of the circle of Willis, such as the carotid and main trunk of the middle cerebral artery, show little change in size during acute mechanical hypertension. The vasoconstriction is accompanied by decreased cerebral blood flow, increased intracranial pressure, and occasional perivascular hemorrhages. The arteriolar constriction produced by this method is not as marked as the arteriolar spasm seen in severe renal hypertension.

2. Cerebral arterial constriction begins when the systolic blood pressure exceeds 180 mm. and is accompanied by brain swelling due to the excessive filtration pressure in the capillary bed. Occlusion of one carotid artery protects the ischemic hemisphere from brain swelling during acute hypertension, but the pial vessels in the distribution of the occluded vessel (collateral circulation) become constricted.

3. In severe, prolonged cerebrovascular hypertension produced by aortic clamping, brain swelling results in cerebrovascular compression, with further cerebral ischemia, brain herniation, and compression of the vasomotor center resulting in more reflex vascular hypertension. Death from brain herniation occurs unless blood pressure is reduced.

4. Mechanical cerebrovascular hypertension alone does not cause "vasospasm." For severe hypertensive vasospasm to occur in the pial arterioles an additional factor, such as a circulating agent that irritates the cerebral arterial smooth muscle excessively must be required.

5. Intravenous injection of purified hypertensin produces severe pial arteriolar constriction, decreased pial blood flow, and hypoxia. Pial arterial constriction persists after the blood pressure has returned to normotensive levels.

Technical assistance for this study was provided by Mr. Peter Miller. Histologic study of stained sections of the brain after necropsy (courtesy of Dr. James Landers) showed no vascular changes other than rare perivascular hemorrhages.

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A simple test of coordination in the fingers

C. Miller Fisher, M.D.

Test for finger coordination

IN ASSESSMENT of the fine motor activity of the upper extremity, a series of tests is commonly employed —holding the arms outstretched, touching the index finger to the nose, rapid pronation-supination of the forearm, touching the thumb to each of the fingers, rhythmic opposition of the index finger to the tip of the thumb, patting and polishing movements of the hand, and handwriting—each examiner having his own favorite tests. These methods cannot fail to detect severe disturbances of motility, but, in the case of minor abnormalities, it often is not easy to decide if the imperfection is significant because either the motion of so many parts makes it difficult to judge the precision with which the maneuver is performed or the movement is so elementary that it can be carried out satisfactorily even in the presence of a certain amount of neurologic deficit. In the search for a bedside test in which the number of parts moved is restricted and in which fair accuracy and good speed can be achieved only by normal persons, the maneuver shown in the figure has been selected.

It consists of tapping the tip of the flexed index finger against the thumb, opposite the distal knuckle (the interphalangeal joint), as rapidly as possible. The upward excursion of the tip of the index finger is ½ to ¾ in. Instructions are not difficult for the patient to understand. Precision on the part of the patient must be insisted upon, and, to help in this, an ink mark is sometimes made to indicate the point to be tapped. Normal persons under the age of 50, sophisticated or not, can usually tap lightly and accurately at a rate of 3 to 5 per second, moving chiefly the index finger; the thumb participates to a much lesser extent. Normally, the dominant side is slightly more agile than the nondominant. While some patients aged 65 or older show a moderate slowing that might be attributable to "aging" of the nervous system, it is not uncommon to find very rapid movements preserved in persons more than 80 years old.

The principal value of the test is as a screening measure in the early stages of a neurologic illness; if the test is well executed, it is unlikely that coordination will be found at fault in the other tests, and, if an abnormality is observed, the patient's actions in the other tests can be more carefully scrutinized. In the past three years, the author has observed an appreciable number of cases in which this test attracted attention to an otherwise overlooked imperfection in the performance of some of the other commonly employed tests and a few cases in which it alone detected a significant

From the Massachusetts General Hospital, Boston.

motor deficit. Possibly, the great sensitivity of the test as an indicator of neurologic disturbance is attributable to the fact that the fine play of many small muscles with a large cortical representation is under observation.

Assuming that peripheral motor weakness is not the limiting factor, several different kinds of abnormality may be encountered—slowness, small excursion, irregular amplitude, dysmetria, premature arrest, and total or almost total inability to carry out a single movement. To be able to analyze each of these abnormal movements would be highly advantageous, but this has been only partially accomplished. In cerebellar disturbances, one sees in the movements of the index finger a rather striking model of dysmetria as the tip of the finger overshoots, undershoots, stops short, or comes down with inordinate pressure. Thus far, in all cases of dysmetria of the movements of the large proximal joints, finger dysmetria was present as well; in other words, cerebellar dysfunction limited to large joints must be quite rare. Familial or senile tremor, a disorder common in mild form and of little significance, must be kept in mind as a cause of dysmetria in this test. In early parkinsonism, the extrapyramidal disorder shows up as an almost total blocking or "freezing" when rapid movements are attempted or the excursion quickly lessens with each successive tap. A mild pyramidal deficit or spasticity first evinces itself in loss of speed, increased movement of the thumb, and radiation of the movement so that the other fingers and even the wrist participate; accuracy is relatively well preserved. A sensory deficit of even moderate severity interferes very little with the test. Children perform the test slowly and irregularly but without dysmetria, indicating that incoordination peculiar to childhood is not in the nature of a simple cerebellar deficit. Very occasionally, a patient with an otherwise healthy nervous system is slow and incoordinate for unknown reasons. Not infrequently, one encounters cases in which the customary battery of tests of coordination does not allow a precise analysis and categorization of the motor deficit in terms of weakness, rigidity, spasticity, cerebellar ataxia, apraxia, or combinations thereof. It is the author's impression that, even in these cases, the test described herein, by virtue of its restricted field of motion, assists in the recognition of a pattern of abnormality.

Congenital malformation of spinal canal with neurogenic bladder

Successful treatment by neurosurgery and transurethral bladder neck resection

Paul B. Jossmann, M.D., Ph.D., Joseph Fischmann, M.D., F.A.C.S., and Cesar G. Tedeschi, M.D.

THE MANAGEMENT of congenital disorders of the spinal canal has been the subject of controversial discussions in recent years. Paul Bucy[1] has stated that "the difference of opinion is not one of neurosurgical methods but one of philosophy." He commented on the alternative between active (surgical) and conservative treatment as follows: ". . . let me emphasize that every child with a congenital spinal malformation, *but without serious neurologic deficiencies* should receive every indicated form of treatment that modern medicine can offer. But no infant with a myelomeningocele with paralysis of the legs and sphincters . . . should receive any care except to feed him. All reparative operations . . . should be withheld."

The following case of a congenital disorder of the spinal canal is reported because of several rare facets of diagnosis, pathology, and treatment which illustrate the complex problem involved.

CASE REPORT

A 33-year-old woman was seen first in December 1952 with the complaint that a congenital abnormality in her lower back had caused a variety of more or less severe symptoms throughout her life. The patient had never been able to lie on her back or sit in a normal position. She also had to wear special garments. Pressure on her lower back caused headaches and even fainting spells.

History. The patient had been born with a large mass in her lower back, which had increased in size during her first ten years but had not grown markedly since. Her parents were told by several physicians that she would hardly survive the first year and that, if she did, she would probably never be able to walk on account of paralysis of the legs. When she was 8 years old, operation was discussed but the consensus of several physicians, including pediatricians and neurologists, was that the risk of an operation and its possible residual effects were far greater than its questionable success. A recent neurologic consultation had resulted in the same advice, not to perform any surgery. Up to her thirteenth year, the patient was catheterized by her physicians, and later by her mother, on the average of four times daily. She then learned to catheterize herself and performed the procedure with exemplary precision every six hours. She never missed carrying with her a sterile catheterizing kit. In spite of the strictest observance of asepsis, severe acute attacks of chills and high temperature occurred repeatedly because of cystopyelonephritis. Even left nephrectomy was considered.

Neurological examination. The patient was medium sized and well built. A mass was noted over the sacral region, measuring about 18 cm. in diameter and protruding about 4 cm. over the surface of the back. Below this mass was a small dimple. On palpation, the mass did not appear to contain fluid but seemed

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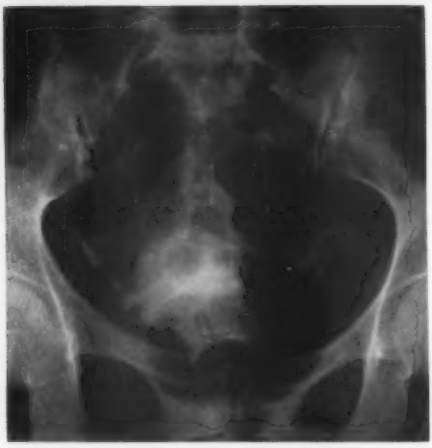

Fig. 1. Note spina bifida and marked distortion of bladder.

to consist rather of a solid, somewhat roughly shaped, nontranslucent mass. Pressure on it produced almost instantaneous headache. No motor deficits were found in the lower extremities, which were normally formed with the exception of bilateral pes cavus. Hypesthesia in sacral regions 3, 4, and 5 was more pronounced on the right side. Knee and ankle jerks were present, normal, and equal. Neurogenic bladder was manifested by inability to void voluntarily and by incontinence. Roentgenograms showed large spina bifida from S3 down the whole sacrum (Fig. 1).

Diagnosis. The history and findings were conclusive for the diagnosis of congenital malformation of the sacral region, probably a meningocele and a large superimposed tumor. In view of the relatively minor neurologic deficits and the extreme inconvenience to the patient caused by the deformity and symptomatology, neurosurgery was considered indicated.

The patient was operated on by Dr. Gilbert Horrax, neurosurgeon at New England Deaconess Hospital, on February 3, 1953. A large lipomatous mass was dissected; the cylindrically shaped root of the meningocele was visualized in the center of the mass and was then separated from the tumor in its entire length. The lipoma was removed. The dural meningocelic prolongation measured about 5 cm. in length and 1.5 cm. in diameter and was tubular. It contained 3 or 4 sacral roots that were adherent in their upper end to the inner aspect of the meningocele. The dural sac of the meningocele was sectioned about 1 cm. above its origin. The lipoma weighed 530 gm. and measured 16 by 13 by 6 cm. Its capacity was about 30 times that of the meningocele.

The postoperative course was uneventful for about one week. Then the cavity left in the sacral region after removal of the lipoma was found to be filled by what seemed to be liquid secretion. On puncture, about 400 cc. of serous fluid was removed, but the cavity refilled. Therefore, on March 3, Dr. Neil W. Swinton, surgeon at New England Deaconess Hospital, did a surgical revision of the site from which the lipoma had been removed. The large cavity was carefully inspected for possible leakage of spinal fluid. No such outlet was found, and the cystic tissue lining was completely excised. After this procedure, a plastic operation was performed in order to reduce the size of the remaining cavity. The postoperative period was uneventful, and the patient was discharged about one week later.

For the next two years, the patient felt greatly relieved by the removal of the tumor. She could lie on her back and sit normally for the first time in her life. Also, she was able to wear regular garments. Her previous fear of instantaneous death if the fluid-containing mass should accidentally burst, mentioned to her as a possibility, had been eliminated.

In contrast to this remarkable general improvement, the urinary incontinence and retention persisted unchanged. Since, in recent years, very satisfactory results had been achieved in repair of bladder control by surgery, the patient was submitted to urologic reevaluation.

The outstanding urologic features of this case were incontinence and almost complete inability since birth to micturate voluntarily, with severe bouts of pyelonephritis and cystitis. The pattern of incontinence was not that of continuous dribbling. Whenever the patient's bladder filled to a certain degree, she involuntarily lost large amounts of urine. However, as catheterization revealed after such incidents, there was 300 to 400 cc. of residual urine. Almost every morning on awakening, she found

her bed soaking wet. She regularly lost large amounts of urine during orgasm.

On April 8, 1955, the patient was admitted to Mount Auburn Hospital, Cambrige, Mass.

Physical examination revealed an essentially normal 34-year-old woman in good general condition. No organs or masses were felt in the abdomen. The kidneys were not palpable. The left kidney was slightly tender on bimanual palpation. A well-healed operative scar was observed in the area of the sacrum. Laboratory tests showed the urine to be light amber and clear, with acid reaction and a specific gravity of 1.022. Albumin and sugar were negative. The sediment contained many white cells, no red cells, numerous mucous threads, epithelial cells, and a few amorphous crystals. The red cell count was 4,200,000 and the hemoglobin 13.5 gm. The white cell count was 16,350 and the nonprotein nitrogen 43 mg. per 100 cc. The Hinton test was negative. Urine culture revealed gamma enterococcus. A phenolsulfonphthalein test revealed 55% excretion in two hours. Intravenous pyelograms showed prompt excretion and good concentration of Urokon in both kidneys. The lower end of the left ureter was not seen on any of the films. Retrograde pyeloograms failed to show any disease in either kidney pelvis. The lower third of the left ureter was slightly uneven in width on the one film on which it was demonstrated. A cystogram showed an unusually elongated bladder, with marked trabeculation, somewhat displaced to the right (Fig. 2).

A cystometrogram revealed gradually increasing pressure up to 30 mm. Hg, with a filling of 300 cc. of fluid, when a few additional cubic centimeters caused an unbearable urge to urinate, with severe pain. The first desire to void occured at a filling of 200 cc. However, it immediately disappeared (Fig. 3). Cystoscopy revealed a bladder wall with extreme coarse trabeculation throughout. The mucous membrane was markedly edematous. Numerous diverticulum-like cellules were noted. After injection of 3 cc. of indigocarmine intravenously, excretion appeared in three and one-half minutes on the right and nine minutes on the left. The concentration was satisfactory on the right but sluggish on the left. The outlet of the bladder appeared to be small and contracted, represented merely by a narrow,

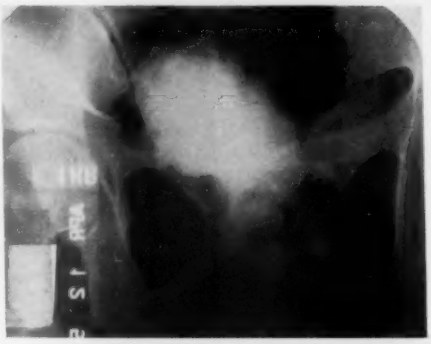

Fig. 2. Cystogram. Note marked trabeculation and distortion of bladder.

rigid ring lacking in both dilating and contracting capacity. A considerable amount of firm, fibrous, sclerotic tissue was palpable between the bladder neck and the vaginal wall, as felt by the examining finger pressed against the cystoscope.

On the basis of the history and the diagnostic data, there was no doubt that the patient had a congenital cord bladder of the autonomic type. The large residuum was caused by neurogenic disturbance in voiding voluntarily and mechanical obstruction of the bladder neck due to extreme fibrosis and hypertrophic changes of the musculature.

As to treatment, the question arose: Which one, if any, of the available surgical repair procedures could and should be applied to alleviate the condition? None of the many

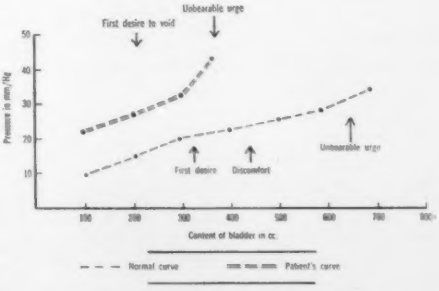

Fig. 3. Cystometrogram. Patient's curve (*upper*) as compared with normal (*lower*)

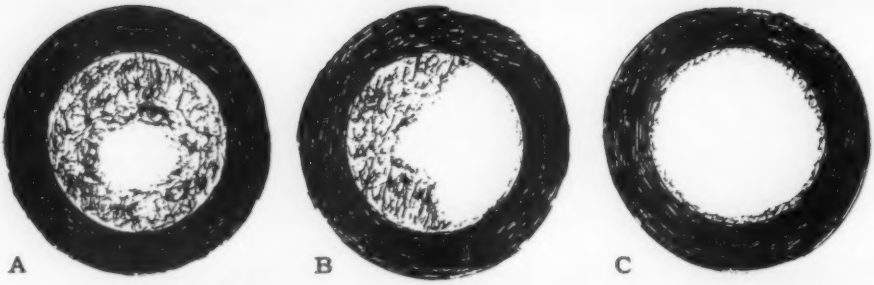

Fig. 4. Cystoscopic sketch of resection. [A] Outlet almost completely blocked by fibrous diaphragm. [B] Left half of diaphragm removed. [C] Procedure completed

sphincter repair methods for incontinence, including suburethral myoplasty (Fischmann), could be considered because of the large residuum and almost complete lack of elasticity of the bladder neck.

Assuming that fibrous bar formation with rigidity of the bladder neck, that is of the sphincter with its markedly reduced lumen, might well be an important mechanical factor in addition to the neurogenic disturbance preventing bladder evacuation, Emmett[2–7] suggested transurethral resection of the vesical neck, a promising procedure for reducing or even preventing residuum formation. Since his gratifying results with various neurogenic vesical dysfunctions and our personal experience with 4 previous cases were encouraging, this operation was done on the patient on April 16, 1955. Under intravenous Pentothal anesthesia, the bladder neck was resected with the MacCarthy resectoscope (Fig. 4). The indwelling catheter was removed on the sixth postoperative day. Immediately after this removal, the patient was unable to void. She was catheterized once for 600 cc. of urine, but, after this, voluntary micturition became the rule. The bladder function improved so rapidly that, by the fourth day after removal of the catheter, the patient's diurnal frequency was normal and she eliminated up to 600 cc. of urine at a time. She had no nocturia or incontinence. She was discharged from the hospital on the eleventh postoperative day with no urinary complaints whatever.

Histologic examination of the removed tissue revealed segments covered by stratified squamous epithelium. The underlying tissue was areolar and fatty, with congested vessels and inflammation. Some areas of hypertrophic muscle tissue were indentified. No cancer was found. However, most of the material was destroyed by charring due to fulguration.

The first postoperative follow-up examination was made in November 1955, seven months after the resection. The patient reported no incontinence, nocturia, increased frequency, urgency, or dysuria. She had no sensation of incomplete emptying of the bladder after voiding. She observed the involuntary loss of a few drips of urine during her menstrual periods for the first two months after the operation, but this also completely subsided thereafter. The urine was negative except for rare white cells in the sediment. Cystoscopy still revealed marked trabeculation but no evidence of cystitis. No residuum was found in the bladder.

The patient has not had pyelitis or pyelonephritis since the operation.

Further reports indicate complete absence of urologic symptoms. The last report, dated March 20, 1958, was made by the patient's physician three years after the operation. She was then free of any urologic disturbances.*

DISCUSSION

The pathologic-anatomic interest of the case lies in the nature, size, and location of the mass removed at operation. As mentioned, the mass consisted of an epidural lipoma 530 gm. in

*Since reading this paper, 6 more patients have been treated with equally satisfactory results.

weight and entirely composed of mature fat cells (Fig. 5). At the point at which this mass was located, there was a bony vertebral defect and the mass itself rested on the outer wall of a clearly identified meningocele (Fig. 6).

The close relation between the lipoma and the meningocele indicates strongly that the two disorders were not accidentally associated but rather linked together in the sense that one disorder, the overabundant proliferation of adipose tissue, was responsible for the occurrence of the other, the meningocele. It is, in fact, very likely that the meningocele resulted from the traction exerted on the spinal cord involucra by the ever increasing mass of fat.

Until approximately the third month of intrauterine life, the spinal cord and the vertebral column approximate each other in length. As the skeletal development progresses, the proportions of these two structures alter and cephalad migration of the cord takes place. At term, the conus medullaris is situated approximately at the level of the fourth lumbar body and, by the end of the growth period, has come to rest opposite the twelfth thoracic or first or second lumbar bodies.

It is, therefore, reasonable to assume that, in the case under consideration, the terminal portion of the cord, anchored by the abnormal anlage of fat, underwent gradually increasing traction as growth progressed. It is further conceivable that, with the accumulation of fat in addition to the original anlage, the traction became proportionately greater and the meningocele larger, thus increasing the neurologic deficit.

Whereas subcutaneous, nontender, poorly circumscribed masses of fat are commonly associated with occult spinal defects,[8] true spinal lipomas are rare. According to Collins and Henderson,[9] they constitute only about 1% of all primary spinal tumors. Their subdivision into 2 distinct groups, intradural and extradural, is sound from the standpoint of different histogenetic mechanisms. Intradural lipomas are especially rare and, since the subdural space is generally considered to be devoid of fat cells, their occurrence has been the source of much speculation. Ehni and Love[10] have discussed the various theories in order to explain the occurrence of lipomas within the dural sac. Presence of fat cells in the pia, enfolding of mesodermal elements in the neural tube during development, and a differentiation into fat cells of the mesenchyma that penetrates the neural wall to lay the framework of the vascularization of the central nervous system have all been suggested to explain the occurrence of both intradural lipomas and other kinds of connective tissue tumors.

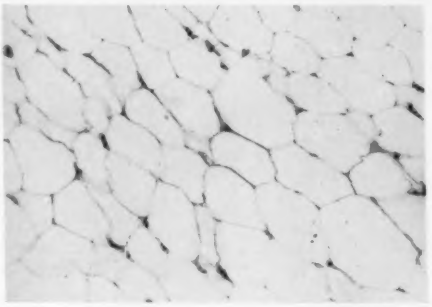

Fig. 5. From the mass removed at operation, showing mature fat cells but no other atypical features

SUMMARY

The case of a 33-year-old woman with congenital malformation of the lower spine is discussed from neurologic, urologic, and pathologic points of view.

Earlier examinations failed to establish the correct diagnosis of a large tumor containing

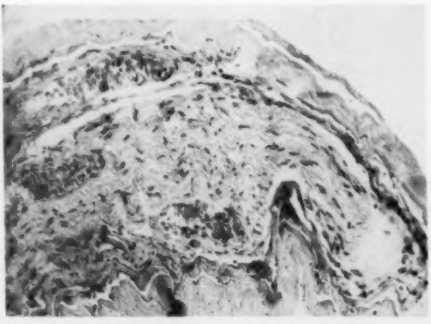

Fig. 6. From the meningocele, including bundles of nerve fibers of the spinal nerve roots.

a small central meningocele. The lesion as a whole was considered to be a large meningocele not suitable for surgery. Removal of a large lipoma with additional surgical repair of the urinary incontinence resulted in a complete cure.

The pathologic-anatomic aspects are also discussed.

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Value of equivocal signs in neurologic diagnosis

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THE TERM equivocal neurologic sign has been in common use since the procedure for routine neurologic examination was first established by our clinical ancestors during the end of the last and the beginning of the present century. From it, one ordinarily deduces that, during a thorough and complete examination of the nervous system, a sign or signs have been noted which suggest neuropathology but which are either so slight as to be uncertain or only occasionally and not consistently present. The fact that these equivocal signs very often appear without any apparent relation to other signs and symptoms that have clearly indicated some structural and functional syndrome adds another uncertainty to their value in neurologic diagnosis. These signs do, however, recur in persistent patterns and with well-defined individual characteristics, so that they have continued to be suspect or equivocal throughout the years.[1] Thus, an exhaustible ankle clonus, an incomplete Babinski dorsiflexion, or a facial tic that may be either habit or the result of an irritation of a nerve pathway is often noted as equivocal.

Another factor has added to the uncertainty of the meaning of such signs, especially during the past twenty years: they occur with greater frequency among persons with emotional disturbances, particularly children,[2] than among persons considered psychologically normal. The relation of such signs to behavior disturbances of children has therefore become the subject of study. The term soft neurologic signs has been utilized to describe the signs associated with more complex motor behavior.[2]

In particular, motor coordination as related to space and body concepts has been analyzed in cerebral cortical injuries of adults[3,11] and in schizophrenia in children.[2] More recently, examination of sensory deprivation or distortion has produced evidence that relates to both concepts of reality and the functional capacity of the central nervous system.

For these reasons, it has seemed of possible value to review the findings made during examination of the central nervous system in a large number of children with behavioral disorders severe enough to have necessitated admission to a mental hospital. Many of these children also have signs of chronic brain injury. The study, which was begun about three years ago, included examination of 355 patients ages 6 to 16 years and 72 control children. Sociologic, psychologic, and psychiatric evaluations of each child were made together with neurologic and physical examinations and electroencephalograms. The present paper is an attempt to correlate the neurologic findings with those obtained by staff members of the other disciplines. Data will be offered which may aid in evaluating equivocal signs and symptoms in relation to structural and functional localization within the central nervous system.

PROCEDURE

The original design of this study, which has been consistently followed to termination, was to examine a group of disturbed children, all inmates of a state mental hospital, according to the various disciplines described above and to then attempt an interdisciplinary correlation of findings. The staff of each unit would examine each child immediately after his or her admission to the hospital and then make whatever independent deductions seemed indicated with regard to diagnosis or etiologic pattern.

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TABLE 1
AGE AND SEX DISTRIBUTION OF CASES

Age	Patients		Controls	
	Boys	Girls	Boys	Girls
13	19	14	5	7
14	27	19	5	8
15	21	6	12	10
16	12	5	10	8
Total	79	44	32	33

Eventually, at staff conferences, the findings of all functioning units were discussed and compared and an over-all descriptive pattern of the child's disorder was made with a view to consequent study and clinical treatment. Summaries have been made, and will continue to be made, from the accumulated material of the various disciplines. The present report is therefore only one of several and has been taken entirely from the social histories, psychologic reports, neurologic examinations, and staff conference notes to be found in the individual case histories at the Mental Health Research Institute.

In all, 123 patients, aged 13 to 16 years, who were admitted consecutively to the hospital between November 1957 and February 1959, had complete neurologic examinations, including the details for equivocal signs. They were all examined by Frederick W. Maire, M.D.,* a most careful and highly trained person, on 1 to 3 occasions shortly after admission. His reports as summarized in the case histories have been carefully examined by the author, and comparison has then been made between his findings and those obtained by other disciplines.

TYPES OF SUBJECTS

The 65 control subjects were selected from cooperating adjacent schools. The staffs were asked to furnish lists of children in grades 7, 8, 9, and 10 who were "successful," that is, children who were in their appropriate grade for chronologic age, were passing, had never repeated a grade, and were "good citizens." From these lists, we picked by rote the number desired. Originally, 9 boys and 9 girls were chosen from each class. Eventually, through various necessities, only 65 of the 72 remained useful for the present study. These control children and their parents cooperated in going through all the tests, questionnaires, and procedures we had used with the patients. The amount of agreeable effort and cooperation on the part of the teachers, the controls, and their families was very great throughout the entire 2 winters of the study. The age and sex distribution of both controls and patients is shown in Table 1.

It should be remembered in the discussion to follow that, although all of the patients were in hospital because of behavior disturbances, all were in good contact with their surroundings and especially with the examiners. The 123 used in this report have been selected from a total of 213 of equivalent age, first, because each child selected was capable of cooperating for the full test battery and, second, because the case history was, in each instance, sufficiently detailed so that full development history could be studied. Of the remaining children not utilized for this report, 9 were too disturbed to produce adequate details on examination, 8 were too low in functioning intelligence, and 73 had a disturbed family history, without adequate information as to etiologic factors.

Psychological testing included Wechsler-Bellevue, Bender-Gestalt, Rorschach, and draw-a-person tests in every instance and was carried out under the direction of psychologist A. E. Schwartsman, Ph.D.†

Electroencephalograms were recorded within a few days of admission on a Grass 8-channel machine with attached Edin frequency analyzer, according to conventional monopolar and bipolar recording. With the exception of 23 epileptic patients and a very few other children who were taking tranquilizer drugs, these children were receiving no medication. If a child was on medication when first examined, subsequent records were always made without medication.

Clinical diagnosis was made at a staff conference held about two weeks after admission, when each unit had completed the individual testing. The diagnostic categories applied were [1] schizophrenia, or thought disturbance; [2]

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TABLE 2

EQUIVOCAL SIGNS IN 123 PATIENTS AGED 13 TO 18 YEARS

Deviancy	No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visual	1	44																	
Extraocular muscle dysfunction	2	5	41																
Tremor	3	16	19	40															
Left dominant	4	13	17	15	34														
Left-right confusion	5	15	15	14	15	32													
Auditory	6	11	8	10	6	7	31												
Intention tremor	7	13	12	12	12	10	5	29											
Reflex	8	11	16	9	9	8	7	8	28										
Athetoid	9	15	11	12	10	9	4	9	13	26									
Speech	10	9	12	11	9	7	5	7	7	6	26								
Hyperactive	11	12	11	12	6	9	2	7	7	12	9	26							
Dysdiadochokinesia	12	12	9	19	8	9	5	5	8	6	6	8	21						
Graphesthesia	13	8	9	4	7	9	2	6	8	10	6	7	11	20					
Babinski	14	10	5	6	3	5	6	9	4	6	2	5	3	5	17				
Nystagmus	15	7	9	5	5	8	5	2	4	4	3	2	1	3	1	15			
Tic	16	5	6	5	4	3	1	3	3	7	2	10	3	5	2	1	15		
Whirling	17	6	4	6	5	7	5	3	3	4	4	4	3	3	3	0	1	14	
Pupils	18	8	6	3	5	8	2	7	4	5	2	4	4	8	6	3	2	4	12
Per cent of total deviancy		36	33	33	28	26	25	24	23	21	21	21	17	16	14	12	12	11	10

TABLE 3

EQUIVOCAL SIGNS IN 65 CONTROLS AGED 13 TO 16 YEARS

Deviancy	No.	1	2	3	4	5	6	7	8	9	12	13	14	16	17	18
Visual	1	18														
Extraocular muscle dysfunction	2	2	8													
Tremor	3	4	3	11												
Left dominant	4	3	2	2	8											
Left-right confusion	5	1	1	1	2	10										
Auditory	6	2	1	1	2	1	8									
Intention tremor	7	0	0	1	0	1	0	3								
Reflex	8	0	1	1	0	3	3	1	9							
Athetoid	9	1	0	1	2	1	1	0	0	3						
Dysdiadochokinesia	12	2	2	4	3	1	2	0	3	1	10					
Graphesthesia	13	2	3	5	2	0	2	4	0	1	2	10				
Babinski	14	2	3	3	1	0	1	3	0	1	0	3	4			
Tic	16	1	0	0	0	0	0	0	0	0	0	0	0	1		
Whirling	17	4	1	1	1	1	1	0	0	0	1	0	0	0	7	
Pupils	18	3	1	1	1	0	0	0	0	0	0	0	0	0	1	4
Per cent of total deviancy		28	12	17	12	15	12	14	5	5	15	15	6	1.5	11	6

thought disturbance with possible organic factor; [3] organic brain disturbance; [4] primary neurosis; [5] neurosis, with questionable thought disturbance; [6] primary acting-out aggression, or sociopath (Tables 3 and 4). These diagnoses were made for purposes of group identification within the research organization and prognostic and therapeutic direction for the patient. They were the combined opinions resulting from the evidence accumulated from case histories as well as from psychologic test results and ward behavior. Neither the electroencephalographic findings nor those of neurologic examinations were used here, since it was felt that neither factor had any clear significance in relation to the organic or nonorganic.

EQUIVOCAL SIGNS

The equivocal signs to be considered in this paper are numbered and listed in the tables according to the frequency of their occurrence

among the 123 patients. Each appeared in 10 or more patients; 3 other signs (catatonia, twice; tongue tremor, twice; and astereognosis, six times) have been omitted. Not all 18 signs appeared in the control group, 3 being entirely absent. Nevertheless, the same numbers have been maintained in the tables on control data. Thus, 1, the most frequent sign, is visual defect in both groups and 14 is equivocal Babinski sign, although some numbers are left out in the control tables (Tables 2 and 3). Definition of these deviancies from normal follows.

Visual defect. On examination with the Snellen chart, vision that was 20/40 or less in one or both eyes was considered as a deviancy. Use of glasses could not be utilized as a sign among our population, since low frustration tolerance among the boys and unwillingness to appear in glasses among the teen-age girls carried much more weight among the patients than among the controls. Comparison by use of glasses therefore had to be ignored, although it was always noted whether the child thought he possessed glasses "somewhere." Visual defect appeared in 44% of patients and 28% of controls.

Dysfunction of extraocular muscles was found in 33% of patients and 12% of controls and varied from marked dysfunction in 3 children who had had earlier operations to disturbance of only one part of eye movement. Thus, a number of children had convergence that was distorted or deviant in one eye only. True paralysis of any single movement or disturbance of a single nerve was not detected. These are the occasional squints and diplopias and, apparently, are much more frequent among children with behavior disturbances than among normal children.

Tremor of extended fingers occurred so frequently and to such marked degree that it was early noted in this series (33% of patients and 17% of controls). A fine, flickering tremor appeared very frequently when these children were attempting fine finger movements, such as writing or drawing. It was always accentuated by tension, a first interview, for example, but remained a consistent finding throughout. If the child stood with arms extended and fingers spread, this tremor became most marked. It was often greater on one side than on the other but always bilaterally present. In some instances, the side of greatest tremor was that in which other signs such as reflex deviancy also appeared.

Left-handed or mixed dominance was included in the deviancies because it has been so frequently associated with such signs as left-right confusion or reading disability. All children in whom dominance was not unequivocally right-sided in hand, foot, and eye have been included in this group. Tests were made for these 3 areas. It was felt that training the child to use the right hand had, in many instances, distorted his or her ordinary use of both hands. Attention was therefore paid only to the result found by tests made here; 28% of patients and 12% of controls showed either strongly left-sided dominance or ambidexterity.

Left-right confusion appeared in 26% of patients and 15% of controls. This test was administered in the usual fashion: the subject was asked to identify left and right areas and then left and right bodily relationships.

Auditory impairment was examined for 2 reasons: the possibility of eighth nerve defect and the possibility of central nervous system involvement via the middle ear. As in the other tests, the signs used here as indicating auditory impairment were mild and often equivocal. Of the entire group, 3 children had known impaired hearing, such that, at school, attention had to be paid to their auditory input. All the rest were unaware of any practical deficit, although, in a few instances, the child and parent knew that he heard better with one ear than with the other as a result of previous middle ear infection. Auditory deficit was noted, in most instances, as inability to detect auditory stimuli as well through one ear as through the other. The differences were usually slight. In a few instances, it was noted that bone conduction might be impaired, but no true nerve deafness was detected. One-fourth of the patients showed some auditory deficit. About half that number, 12% of controls, also had such changes.

Intention tremor here means an increase in dyscoordinate alternate movements as directed movement is being completed. In most instances, this was seen during the finger-to-nose or finger-to-finger test. In many also, heel-to-knee testing revealed the same type of jerky dyscoordination. Again, as with tremor, de-

viancy was often greater on one side than the other but, in most instances, was bilateral. It resembled in many ways the true cerebellar intention tremor and, at times, was related to past-pointing also. But, being a true equivocal sign, it also frequently varied greatly in degree on repeated examination. It was found in 24% of patients and only 5% of controls.

Reflex asymmetry was noted in a surprising number of children (23% of patients and 14% of controls). Deep reflexes on one side would be found to differ from those on the opposite side. Occasionally, the difference would be confined to only one extremity but more often involved reflexes of both extremities and, at times, the abdominal reflexes as well. These differences were consistent on repeated examination. The question of mild polio was considered when reflex response was hard to elicit but, as far as history could contribute, was not found significant. Reflexes were diminished or increased but seldom totally absent.

Athetoid movements appeared in 21% of patients and 5% of controls. They were usually associated with fine finger tremor and often with dysdiadochokinesia. On effort, typical athetoid finger, wrist, and arm movements appeared. Occasionally, body twisting was observed in the same patient.

Speech defect never occurred in the control group but was found in 21% of the patients. All types of defect have been grouped together here. Congenital aphasia was noted in 1 child, but none of the others showed true organic etiologic factors. The defect varied from a lisping, baby-talk sort of elision of words (15 cases) to true stammering or stuttering (11 cases). Many of the children, including these last, had had speech training in school.

Hyperactivity is a symptom commonly noted in children with organic defects and behavior disturbances but is difficult to define. In the present series, it was noted as restlessness and increased motor activity during the time of examination. Movements of the hands, especially in relation to other body parts, scratching, nail biting, and touching or tearing objects were most frequently a part of it. Inability to remain still, searching and exploring the room, and general restlessness were other parts. Hyperactivity was never observed among the controls but appeared in 26 patients (21%).

Dysdiadochokinesia. Although dyscoordinate motor activity was noted on examination in only 17% of patients and 15% of controls, poor muscle coordination of this and other types is conspicuous in behavior disturbances. These children are seldom if ever able to compete successfully in athletics at school. Writing or drawing is often notably poorly performed. It is felt that the dysdiadochokinesia described here is a part of poor coordination. For the upper extremities, it was detected as a difficulty in rhythmic movements, such as tapping on the table with the fingers. In the lower extremities, skipping or hopping on one foot revealed the same type of deficit.

Graphesthesia was found in 16% of patients and 15% of controls. It was defined as inability to detect the form of various symbols as "drawn" on the skin. The deficiency was most often less marked on one side, cheek, or palm than on the corresponding area of the other side.

An equivocal **Babinski sign** is one of the common findings in adult neurologic examinations. In the children, it consisted of any type of dorsiflexion of the great toe, with or without fanning of the lesser toes, which occurred repeatedly, although it was often exhaustible. Many times, the sign appeared on first stimulation but was not present after a number of equivalent stimuli. In this test, the positive finding was always unilateral. In about half the cases, deep reflex dyssymmetry was also noted.

Nystagmus. In these patients, nystagmoid, irregular, jerking movements of the eyes occurred when the child looked to the side or, occasionally, to the side and up. The movements were frequently greater to one side than the other. They always appeared when the eyes first moved in the required direction, but, unlike the more intense types seen, for example, on vestibular stimulation, these movements usually appeared only during the first seconds after movement of the eye. It is of interest that they were frequently associated with defects in extraocular movement and occurred in 15% of patients but never among the control children.

Tic or grimacing was noted 15 times in patients and once in the control group. Again, as in other tests, the type of facial distortion

TABLE 4

NEUROLOGIC DEVIANCIES AND CLINICAL DIAGNOSIS

		Schizophrenic	*Schizophrenic ? organic*	*Organic*	*Neurotic*	*Neurotic ? Schizophrenic*	*Sociopath.*	*All patients*	*Deviancies 0-3*	*Deviancies 4 or more*
Visual	1	11	12	11	2	4	4	44	20	24
Extraocular muscle dysfunction	2	7	10	8	4	10	2	41	12	29
Tremor	3	10	8	9	5	4	4	40	13	27
Left dominant	4	7	3	6	4	8	6	34	15	19
Left-right confusion	5	4	9	5	4	6	3	32	8	24
Auditory	6	4	7	4	4	7	6	31	16	15
Intention tremor	7	11	4	6	0	3	3	29	10	19
Reflex	8	3	7	7	3	4	2	28	10	18
Athetoid	9	8	6	7	0	4	1	26	3	23
Speech	10	5	5	7	5	2	2	26	10	16
Hyperactive	11	6	5	8	1	3	3	26	4	22
Dysdiadochokinesia	12	5	7	5	0	1	3	21	17	4
Graphesthesia	13	3	8	4	0	3	2	20	1	19
Babinski	14	3	4	4	1	2	2	17	4	13
Nystagmus	15	1	3	6	1	3	1	15	6	9
Tic	16	2	4	3	3	2	1	15	4	11
Whirling	17	2	3	2	3	3	1	14	6	8
Pupils	18	0	5	4	0	4	0	13	2	11
All patients		20	21	20	19	22	21	123		
Deviancies: 0-3		10	6	8	15	13	18	70		
4 or more		10	15	12	4	9	3	53		
None		0	0	1	6	2	4	13		
Total deviancies		92	110	106	40	73	46	472		
Deviancy per patient		4.60	5.24	5.3	2.11	3.32	2.19	3.84		

TABLE 5

PER CENT OF DEVIANCIES IN CLINICAL CATEGORIES

		Schizophrenic ? Schizophrenic		*Organic ? Organic*		*All neurotic*		*All patients*		*Controls*	
		No.	%	No.	%	No.	%	No.	%	No.	%
Visual	1	15	36	21	51	6	15	44	36	18	28
Extraocular muscle dysfunction	2	17	41	18	44	6	15	41	33	8	12
Tremor	3	14	33	17	42	9	23	40	33	11	17
Lef dominant	4	15	36	9	22	10	25	34	28	8	12
Left-right confusion	5	10	24	14	34	7	18	32	26	10	15
Auditory	6	11	26	11	27	10	25	31	25	8	12
Intention tremor	7	13	31	10	24	3	8	29	24	3	5
Reflex	8	7	17	14	34	5	13	28	23	7	11
Athetoid	9	12	29	13	32	1	3	26	21	3	5
Speech	10	7	17	12	29	7	18	26	21	0	0
Hyperactive	11	9	21	13	32	4	10	26	21	0	0
Dysdiadochokinesia	12	6	14	12	29	3	8	21	17	10	15
Graphesthesia	13	6	14	12	29	2	5	20	16	10	15
Babinski	14	5	12	8	20	3	8	17	14	6	9
Nystagmus	15	4	10	9	22	2	5	15	12	0	0
Tic	16	4	10	7	17	4	10	15	12	1	2
Whirling	17	5	12	5	12	4	10	14	11	7	11
Pupils	18	4	10	9	22	0	0	13	10	5	8
No. patients		42	100	41	100	40	100	123	100	63	100
Without deviancies		2		1		10		13		20	
Total deviancies		164		214		86		472		115	
Deviancies per patient		3.91	5.22	2.15	3.84	1.77					

might differ in different patients. However, a sudden twitching jerk of a part of the face or neck, which appeared to be involuntary and which was always markedly increased when the subject was tense or anxious, was always noted.

Whirling. The test orginally described by Bender[2] was administered here even though it is well known that, in children past the age of about 12, the test has little significance. It was felt, however, that, since children aged 6 to 16 would eventually be examined and since many of these older children had characteristically immature physical and psychologic patterns, the test should be used. The patient, standing quietly with eyes closed, was touched on the top or sides of the head by the examiner, who turned the head one way or the other. The whirling phenonemon consists of the subject following this stimulus by a turning and whirling of the body in response to this relatively slight suggestive stimulus; 14 patients (11%) and 7 controls (11%) responded in this way.

Pupillary inequality. All patients and controls showed prompt response of pupil diameter to light stimulus and other conventional tests. However, 12 patients and 4 controls showed some inequality of pupil diameter and sluggish reaction when the pupillary reflexes were examined in dim light.

FINDINGS

Individual deviancies. The term deviancy has been adopted as indicating an equivocal neurologic sign. Tables 2 and 3 show the relative frequencies at which these deviancies occurred in the patient and control groups. Far fewer were found among the controls than among the patients, but there appears to be a sort of continuum from the patients to the controls. Some of the deviant traits show marked differences between their incidences among patients and controls. Extraocular weakness, tremor, reflex inequalities, athetoid movements, and tic are all markedly more frequent in the patient group. Left handedness and auditory dysfunction are also far more common among patients than among controls. Dysdiadochokinesia, graphesthesia, and whirling, in contrast, occur about as frequently in one group as the other. Speech difficulties, hyperactivity, and nystagmus are not found among children in the control group.

Deviancy syndromes. An attempt was made to group deviancy factors into syndromes. Thus, left-right confusion, left handedness, and speech difficulties or nystagmus, extraocular dysfunction, and auditory dysfunction might relate. However, no effort we could devise produced any significant findings with regard to specific syndromes or significant groups of deviancies beyond those shown by frequency of simultaneous occurrence in Tables 2 and 3.

Correlation with clinical syndromes. When an attempt was made to relate deviancies to suggested organic defect as the etiologic factor in the behavioral syndrome, meaningful correlations appeared. In Table 4, the number of deviancies and the type have been related to the 6 clinical syndromes described above. An average of 5.3 deviancies per person was found for those children with known organic signs and symptoms as obtained from history and clinical observation and 5.24 deviancies per person in the group with both thought disturbance and organic signs. Only 2.19 deviancies per person were noted in the sociopath group and 2.11 in the neurotic group, these patients having thought disturbances without organic defect, with the schizophrenic children lying in between. In Table 5, the clinical syndromes have been divided into 3 larger groups. All children with thought disturbance or possibility of thought disturbance without sign of organic etiology have been placed in column 1. All children with signs or questionable signs of organic defect are grouped in column 2. In column 3 are the neurotics and sociopaths, that is, the patients who are neither organically defective nor psychotic. The differences in number of deviancies per person remain marked and are even more extreme when compared to the findings in the control group listed in column 5.

Some of the deviancies appear as often among controls as among the other 3 groups. Whirling is the most marked of these and cannot therefore be utilized as diagnostic in this series. However, it should be noted here that 9 of the 14 children showing whirling were 13 years old. Since Bender,[2] who has done most to relate whirling phenomenon to early psychotic disturbances in children, states that

TABLE 6
DEVIANCY CORRELATIONS

		IQ				Organic in psychology	Electroencephalogram abnormal	Electroencephalogram normal (staple)	Reading capacity	
		79—	80-89	90-110	111+				Low	High
Visual	1	18	9	15	2	16	16	17	14	6
Extraocular muscle dysfunction	2	8	12	17	4	13	20	12	16	4
Tremor	3	9	14	16	1	16	14	16	15	1
Left dominant	4	6	7	19	2	10	14	10	17	2
Left-right confusion	5	9	12	11	0	10	11	9	18	0
Auditory	6	6	7	15	3	8	15	12	6	5
Intention tremor	7	8	6	13	2	7	13	11	10	3
Reflex	8	5	9	11	3	11	10	10	9	2
Athetoid	9	11	6	8	1	11	10	8	9	1
Speech	10	9	7	10	0	11	9	5	12	0
Hyperactive	11	7	11	7	1	13	11	7	9	0
Dysdiadochokinesia	12	9	5	6	1	11	10	9	8	2
Graphesthesia	13	10	5	5	0	10	9	5	8	1
Babinski	14	3	6	7	1	6	6	5	4	1
Nystagmus	15	6	4	5	0	7	7	6	5	0
Tic	16	5	5	4	1	5	5	3	3	0
Whirling	17	3	6	5	0	6	5	1	6	2
Pupils	18	4	2	6	0	6	3	2	6	0
Total points		30	33	48	12	35	46	45	40	8
Total deviancy		136	133	180	22	177	188	148	175	30
Deviancy per patient		4.53	4.03	3.75	1.83	5.06	4.09	3.29	4.38	3.75

the significance of the phenomenon disappears after about the age of 12, when pseudowhirling phenomena may appear, these data probably confirm this fact.

Auditory disability is distributed equally throughout all patient groups, although to less degree among controls. In the light of histories obtained for the patient group, this might be taken to indicate merely the underprivileged status of the patients as compared to controls. Many more of the former came from broken or poor homes and therefore might be expected to contract earache that was subsequently poorly treated. It is of interest that a greater number of schizophrenic children are left handed than are any other group, although the significance of this is unknown. Other signs such as intention tremor, athetoid movements, and hyperactivity appear almost entirely among the patients with organic defect or thought disturbance, but only unequal reflexes and the Babinski sign have a significantly greater incidence among organically defective than among psychotic children.

Correlation with other signs of organic defect. In Table 6, an attempt is made to show significant relationships between the deviancy characteristics and other findings. Since, in our series, organic brain disturbance has been found to relate to low intelligence as well as to thought disturbance,[7] the number and type of neurologic deviancies have here been related to IQ level. In the borderline and dull normal levels, number of deviancies per patient is relatively high. In the superior intelligence group of 12 patients above 110, there are less than 2 deviancies per person, suggesting that organic factors may be minimal there.

In Table 6, incidence of organic defect as diagnosed purely by psychologic test material is also recorded for comparison with the diagnosis of organic damage made by clinical means, as shown in Tables 4 and 5. In every instance here, organic signs appeared in the Bender-Gestalt test, or the Wechsler-Bellevue, or both. There are 5.06 deviancies per person in the 35 patients designated organically defective by these means. This incidence is very

high and is comparable to the 5.22 deviancies per person which were noted when clinical diagnosis of organic defect was made.

In Table 6, those children with abnormal electroencephalograms are compared with those having stable and normal electroencephalographic records without any sign of dysrhythmia. With the possible exception of extraocular dysfunction, no single deviancy was noted more frequently in children with abnormal electroencephalograms than in those with normal records. Therefore, the deviancy signs found in this series do not appear to relate to any focal or nonfocal pattern in cerebral cortical activity as shown by electroencephalogram.

Because reading disability is very high among the patients (33%), reading disability of two years or more below the expected grade level has been charted together with the findings for the 8 patients with reading levels more than two years above expected grade level. It is possibly significant that left-right confusion, left handedness, and speech difficulty are slightly higher among the poor readers. The number of deviancies in the disabled group is 4.38 per person, while the number among the 8 more able readers is 3.75.

Table 7 presents the data for intelligence level, electroencephalographic abnormality, and reading level for the control group. Since no controls had intelligence levels below 90 and only 4 had slight degrees of reading retardation, little if any differences in deviancy patterns might be expected.

TABLE 7

IQ, ELECTROENCEPHALOGRAPHIC, AND READING LEVEL DATA FOR 65 CONTROLS

		IQ		*Electroencephalogram*		*Reading*	
		90-110	*111+*	*Abnormal*	*Normal*	*Average*	*High*
Visual	1	11	6	5	13	12	6
Extraocular muscle dysfunction	2	7	1	6	2	6	2
Tremor	3	10	1	7	4	7	4
Left dominant	4	6	2	5	3	6	2
Left-right confusion	5	7	1	5	5	7	3
Auditory	6	6	1	3	5	7	1
Intention tremor	7	3	0	1	2	1	2
Reflex	8	4	5	1	6	3	4
Athetoid	9	3	0	1	2	3	0
Dysdiadochokinesia	12	10	0	6	4	9	1
Graphesthesia	13	8	2	5	5	8	2
Babinski	14	3	3	3	3	3	3
Tic	16	1	0	0	1	1	0
Whirling	17	6	1	4	3	7	0
Pupils	18	4	0	2	3	5	0
No. of cases		47	18	25	40	48	17
No. of deviancies		89	23	54	61	85	30
Deviancy per patient		1.89	1.28	2.16	1.53	1.77	1.76
Without deviancy		13	7	7	13	15	5

TABLE 8

CLINICAL DIAGNOSIS AND ORGANIC SIGNS

		IQ			*Electroencephalogram*		*Reading*	
	79—	*80-89*	*90-110*	*111+*	*Abnormal*	*Normal*	*Low*	*High*
Schizophrenic	8	3	9	0	8	8	5	1
Schizophrenic ? Organic	11	4	6	0	11	5	5	3
Organic	9	7	3	1	12	4	9	2
Neurotic	1	5	10	3	3	10	5	1
Neurotic ? Schizophrenic	1	9	9	3	7	9	9	0
Sociopathic	0	5	11	5	5	9	7	1
All	30	33	48	12	46	45	40	8

Table 8 has been added to give information on the interrelationships between low intelligence and organic defect in disorders of behavior. The incidence of borderline or dull normal intelligence is very high among those patients with organic signs and symptoms and somewhat high among those with signs of thought disturbance who are either psychotic or questionably psychotic. Abnormal electroencephalograms are significantly frequent in these same groups and very infrequent in the neurotic and sociopath groups. Reading disability has little if any such relationship.

DISCUSSION

The details relevant to the signs of central nervous system deviancies which are often termed equivocal have been presented together with extensive tables because it is felt that they demonstrate that these signs may be meaningful in relation to organic syndromes. Their incidence among children with disorders of behavior may be of particular significance in light of the present increase in such disorders linked with signs of organic brain injury. Since, in the United States at least, head injury, antibiotics, and improved obstetric and postnatal care are presently furnishing us with a great increase in known organic brain disturbances as the result of trauma, febrile illness, or anoxia, it is likely that improvement in differentiating among various signs will be useful for some time to come. Furthermore, the present uncertainty in diagnosis of other types of psychologic deviancies among children at home, in school, and as related to juvenile delinquency increases the need for diagnostic and prognostic accuracy.

The first question that arises in relation to these data is whether these deviancies are true and consistent signs or merely occasional traits that cannot be usefully related to etiology, prognosis, or therapy. To this author, the present data seem to indicate that the deviancies are true and useful signs. They occur in the present series as persistent single signs and in constellations that are related, in some degree at least, to other signs of organic damage, such as those obtained from clinical history, psychologic findings, and behavioral pattern. They are, furthermore, relatively infrequent in a group of normal controls and among those patients admitted to the hospital for behavioral disturbances related only to neurotic and sociopath patterns. Furthermore, these signs appear most frequently among the more severely damaged children, often of inferior intelligence, and among those with the most long-standing behavioral deviancy.

The question of localization of the focal area or areas within the central nervous system which may have sustained injury becomes of interest also. Many of the deviancies are lateralized, especially those occurring with significant frequency among the patients with organic symptoms. Lateralization of tendon reflex differences, Babinski sign, pupil inequality, and the various types of tremor, athetoid movements, and intention tremor has been persistent in a high percentage of cases. This lateralization might originate at any level from cord to cerebral cortex. Since it is always related to mild signs and never appears as a true defect on conventional neurologic examination, localization within the cord is unlikely because the type of organic defect produced by lesions there usually results in true pareses or marked, persistent sensory defect. Furthermore, the nature of the deviancy is not that which would be expected to be produced by a cord lesion, since the signs are usually related to complex and probably learned activity. However, they are all related to generalized, and usually postural, reflexes or adaptation. Finger tapping, hopping, graphesthesia, and left-right discrimination all require complex and coordinate adjustments but are not the type of discreet voluntary activity or sensory appreciation usually associated with the sensorimotor cortex. This type of deviancy should be associated with an older portion of the brain relating to postural complexities, possibly the basal ganglia or central brain stem.

Other factors exist which might confirm such a placement. Some of these children have had encephalitis known to select these regions. The reticular activating system may be suspect because of the high incidence of fluctuations in consciousness. In addition to the 23 who have known epileptic seizures, there are many who have paroxysmal behavioral patterns, usually related to rage and frustration. Many others, notably among those with schizoid pat-

terns, have periods of greater or lesser contact with reality. Since, as shown above, the incidence of the equivocal neurologic deviancies is higher among pure psychotics than among the neurotic population, the possibility of such a relationship is worth of note.

Electroencephalographic abnormalities are far more frequently related to both organic brain dysfunction as shown by clinical means and low level of intelligence (Tables 5 and 7) than to deviancy pattern, perhaps because the major structural area responsible for the deviancies is both subcortical and in an area that commonly has little direct effect on the electroencephalogram.

The defects in sensory discrimination require special discussion here. Discrimination was tested because other authors had previously found defects in these areas.[2,9,10] Stereognostic sense, not recorded above, was defective in a few instances, but graphesthesia, the perception of an even finer discriminative sensory pattern, was more markedly affected and discrimination between left and right body parts was even more frequently deviant. These deviancies are most specific and could relate, as noted by others, to reading disability.[4,8] They have been discussed in relation to thought disturbances in the child, as significant of the failure to establish self-identity, and to the separation and formation of the ego in the schizophrenic child.[5,6] Together with a defect in detection of multiple simultaneous stimuli, they have been found in brain-injured children by Teuber and Morris Bender[3,11] as well.

Factors in the etiology of the deviancies must be considered. In the present series, not much can be added to the above data, which show that neurologic deviancies occur predominantly among children with other signs and symptoms of brain injury. A careful history of head injury, with or without unconsciousness, has produced nothing significant. All the boys have had blows on the head, as have many of the girls. Appraisal of the resultant loss of consciousness has been impossible from the histories given. Only a few children have been unconscious for a period necessitating hospitalization. Birth histories are equally vague, although, among these patients, prematurity and difficult birth is probably higher than among the normal population. Only 5 have been said to have had "brain fever."

Convulsions occurred at some time in 23, and 1 is congenitally aphasic, as noted above. Again, possibly because of incomplete histories, an attempt at relating age at onset to deviancies produced nothing significant.

Finally, returning to the original title of this paper, of what value are these minor signs of central nervous system deviancy which, although certainly without significance in the production of gross physical handicaps, occur consistently among children with disorders of behavior? There are many psychologic implications but also many that relate to the organic. At the present time, a rapid increase in our knowledge of the effects of sensory deprivation on the individual suggests that it produces, in addition to impaired relationships to reality, a true loss of sensory perception which may be enduring. As yet, we have no information with regard to similar effects in children. It is obvious, however, that the division between clear and present reality and delusional unreality is far less defined in the young child under any circumstances. If, then, in certain children, sensory input becomes distorted or impoverished through structural deviancies, behavorial distortions should follow. Similarly, structural deviancies occurring at the level that may integrate complex learned patterns of motor adjustments may contribute to behavioral distortions. Therefore, it is very likely that further study of the syndromes relating to the minor deviancies of central nervous system function will provide additional information that will be of psychologic diagnostic value.

One field for such study should be that of training. Some evidence, particularly in relation to the reading disabilities and speech dysfunctions, already indicates that specific training can improve function. Training to ameliorate perceptive defects, visual and auditory as well as somatic, and to improve fine motor skills might produce satisfactory changes in the degree of development and maturation of these patients. Its effect should also be examined in the less successful of the normal population, who, although they may never require hospitalization, remain potentially handicapped at the present time.

CONCLUSIONS

1. From the above data, it would appear that equivocal signs of central nervous system dysfunction must be true signs of organic disability because they appear consistently in a single patient and are of similar pattern among groups of patients.

2. These signs may also have some relationship to behavioral patterns in children.

3. A positive correlation exists between diagnosis of organic defect made through clinical means, history, behavioral pattern, and psychologic findings and the equivocal neurologic deviancies, which must, therefore, be considered of value in relation to type of behavioral disorder.

4. No such consistent correlation was found between type and number of neurologic deviancies and electroencephalogram type.

5. Reading disability, which occurs in about one-third of the patients, does not show marked correlation with neurologic deviancy.

6. Low intelligence level among the patients correlates with both frequency of neurologic deviancy and organic brain disorders as diagnosed by other means.

7. Certain neurologic deviancies occur more frequently and appear more strongly related to organic defect. These are bilaterally unequal deep reflexes, equivocal Babinski, intention tremor, hyperactivity, and athetoid movements.

8. Whirling and auditory disability of mild degree do not appear to be related to other organic signs.

9. Since all these equivocal signs are without practical value in relation to physical deficit and appear in individuals whose basic organic neurologic examination is otherwise within normal limits, they must be considered as relating to regions integrating complex adjustments rather than simple motor or sensory function. Their localization within the central nervous system is discussed.

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CASE REPORT

Sudanophilic leukodystrophy with increased hexosamine content

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THE DEMYELINATING diseases that are grouped together under diffuse cerebral sclerosis have been divided on the basis of staining reactions into [1] sudanophilic, [2] metachromatic, PAS-positive, and [3] nonmetachromatic, PAS-positive.[1] One of us (J.N.C.) has shown that the chemical analysis of the involved brain tissue reveals significant differences among these groups.[2] The presence of cholesterol esters and a normal hexosamine content characterizes the involved white matter of the sudanophilic group. In the metachromatic group, however, no cholesterol esters are found, and there is a pronounced increase in the hexosamine content.

The case reported here is unusual in that it belongs to the sudanophilic type histologically but, chemically, had certain features of both the sudanophilic and metachromatic types.

CASE HISTORY

A Polish man was certified to a psychiatric hospital at the age of 37 and remained there until his death at 44. His first symptoms appeared when he was 30 years old. While serving with the Britsh Army in the Middle East, he complained of a feeling of "deadness and heaviness" of his legs and feet during the mornings. Although this became worse, he remained in the army. At age 33, he occasionally lost control of his feet and fell, especially when marching down hills. He was discharged from the Army at age 34 and, having passed the routine physical examination, immigrated to Canada.

He was admitted to a hospital at the age of 35 with complaints of numbness of both lower extremities, particularly the left, and of some unsteadiness in gait. No family history of a similar disorder was known. No abnormality of the cranial nerves was documented. Gait was described as being "spastic-ataxic" Moderate weakness of the muscles of both lower extremities was observed, but there was no muscle wasting. The deep tendon reflexes were increased bilaterally, with upgoing toes on plantar stimulation. The abdominal reflexes were absent. The finger-nose test was done normally, but the heel-knee test demonstrated considerable ataxia. Patchy hypesthesia and reduced vibration and joint position sense were found distally in the lower extremities. The cerebrospinal fluid was clear and without cells, and the protein was recorded as 46 mg. per cent and, on another occasion, as 60 mg. per cent.

At age 37, he was certified to a psychiatric hospital because of personality changes. His behavior was described as silly and sexually aggressive. During the seven years he spent in this institution, he showed emotional lability, a progressive deterioration of intellect, and increasing spasticity, particularly of the lower extremities. Six months before his death at age 44, he became bedridden, very quiet, and almost blind. No further clinical details of his illness were available.

PATHOLOGIC FINDINGS

The brain, spinal cord, and portions of viscera were taken from the embalmed body,

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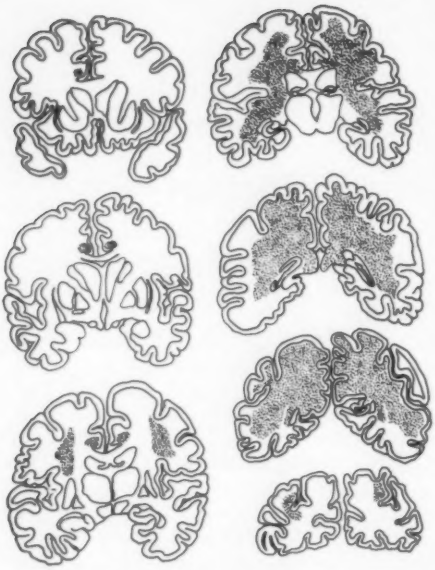

Fig. 1. Diagrammatic representation of the extent of the abnormal white matter as seen in coronal sections

which had been sent to the University of Saskatchewan for dissection by medical students. Immediately after death, the body was placed in a refrigerator. Five days after death, embalming was carried out in the following manner: ½ gallon of a mixture of equal parts of water and embalming fluid (Kosmos) were injected into the femoral artery. The femoral vein was opened during this injection. Then the vein was ligated, and 1 gallon of the following mixture was injected into the femoral artery: 2 parts of Introfiant embalming fluid, 2 parts of liquified carbolic acid, and 4 parts of water. The embalming fluids, Kosmos and Introfiant, are products of Dodge Chemical Co., Boston, and, according to the manufacturer, contain only formaldehyde and alcohol in different concentrations. After embalming, the body was again placed in a refrigerator, where it remained until the brain and other organs were removed three weeks later. These were kept in 10% formalin until histologic investigation and chemical analyses were carried out. The latter were performed about nine months after removal of the brain.

MORPHOLOGIC FINDINGS

When the fixed cerebral hemispheres were cut coronally, sharply outlined areas of grayish-mauve discoloration were seen in the white matter of the parietooccipital lobes (Fig. 1). The characteristic features of these lesions were their symmetry, their sparing of the gray matter and U fibers, and their sharp line of demarcation from normal tissue. Cross sections of the brain stem revealed no gross abnormality.

Large coronal sections through 3 levels of 1 cerebral hemisphere and routine slides from various portions of the brain and spinal cord were made. The paraffin and frozen sections

TABLE 1

STAINING REACTIONS OF MACROPHAGES

Paraffin		Frozen	
Method	*Color*	*Method*	*Color*
1. Hematoxylin-eosin	pink	1. Sudan III	brick red
2. Cresyl violet	blue	2. Sudan IV	brown
3. Heidenhain	bluish-black	3: Toludine blue	bluish-brown
4. PAS	red	4. Methylene blue	blue
		5. Schmorl's thionine	violet-light brown
		6. Reids E.M.B.	blue
		7. Sudan black	gray-brown
		8. Nile blue	light blue
		9. Cresyl violet (Hirsch and Peiffer)	mauve

were stained by various methods as listed in Table 1.

The regions of the cerebral hemispheres which appeared discolored in the gross specimen were completely demyelinated (Fig. 2) and showed nearly complete loss of axon cylinders. The normal white matter was replaced by a fine network of interlacing fibers containing many reactive astrocytes (Fig. 3A).

In the borders of the demyelinated regions were numerous blood vessels surrounded by cuffs of lymphocytes and macrophages (Fig. 3B). In addition, these cells penetrated the vessel walls themselves. Many macrophages and lymphocytes also were found free, without relation to blood vessels; they were less numerous in the center of the abnormal white matter. Comparison of these regions with normal white matter showed a generalized severe loss of cellularity.

The cytoplasm of the macrophages had the staining reactions listed in Table 1. In many instances, no nuclei in these PAS-positive cell-like structures could be identified, and, therefore, it is possible that some of the breakdown products fo myelin were extracellular. Under polarized light, the macrophages surrounding the blood vessels at the periphery of the involved white matter were birefringent (Fig. 3C). No birefringent material was seen centrally. Similarly, sudanophilia of the macrophages was seen only at the periphery of the lesions.

The cortex adjacent to the involved white matter was unremarkable, and it appeared that the advancing edge of the demyelinating process was limited by the deepest cortical layer (Fig. 3D).

In the brain stem, at the level of the inferior olive, were two areas of demyelinization (Fig. 4A). In the chromatic stains, the demyelinated regions showed loss of oligodendroglia with preservation of nerve cells and axon cylinders. No macrophages were seen, and there was no inflammatory response except for a minimal increase in small round cells at the border of the plaque (Fig. 4B).

Fig. 2. Demyelinization of the white matter of the occipital lobe with sparing of the U fibers and optic radiations. Heidenhain stain

CHEMICAL FINDINGS

Portions of the cerebrum and some organs were examined. Areas of apparently normal white matter and cortex, together with a portion of obviously demyelinated cerebral white matter from the center of the lesion, were removed and subjected to chemical analysis.

All material was fixed by embalming and preserved in 10% formalin before analyses were performed. The chemical methods employed were those previously used.[2,3] Water content was obtained by drying portions of tissue at 95° C. to constant weight. Lipid extracts were obtained by following the procedure of Johnson, McNabb, and Rossiter.[4] The P contents of total phospholipids and monoamino phospholipids (hence, indirectly, sphingomyelin content) were estimated by the method of Fiske and Subbarow[5] after the isolation procedures of Johnson, McNabb, and Rossiter had been performed. Cerebrosides were estimated on the assumption that the hexose was galactose; the technic was based on the method of Brand and Sperry.[6] Total and free cholesterol were estimated by the method of Sperry and Webb.[7] Total hexosamine and neuraminic acid were estimated by the methods detailed by Cumings,[2] and neuraminic acid was converted

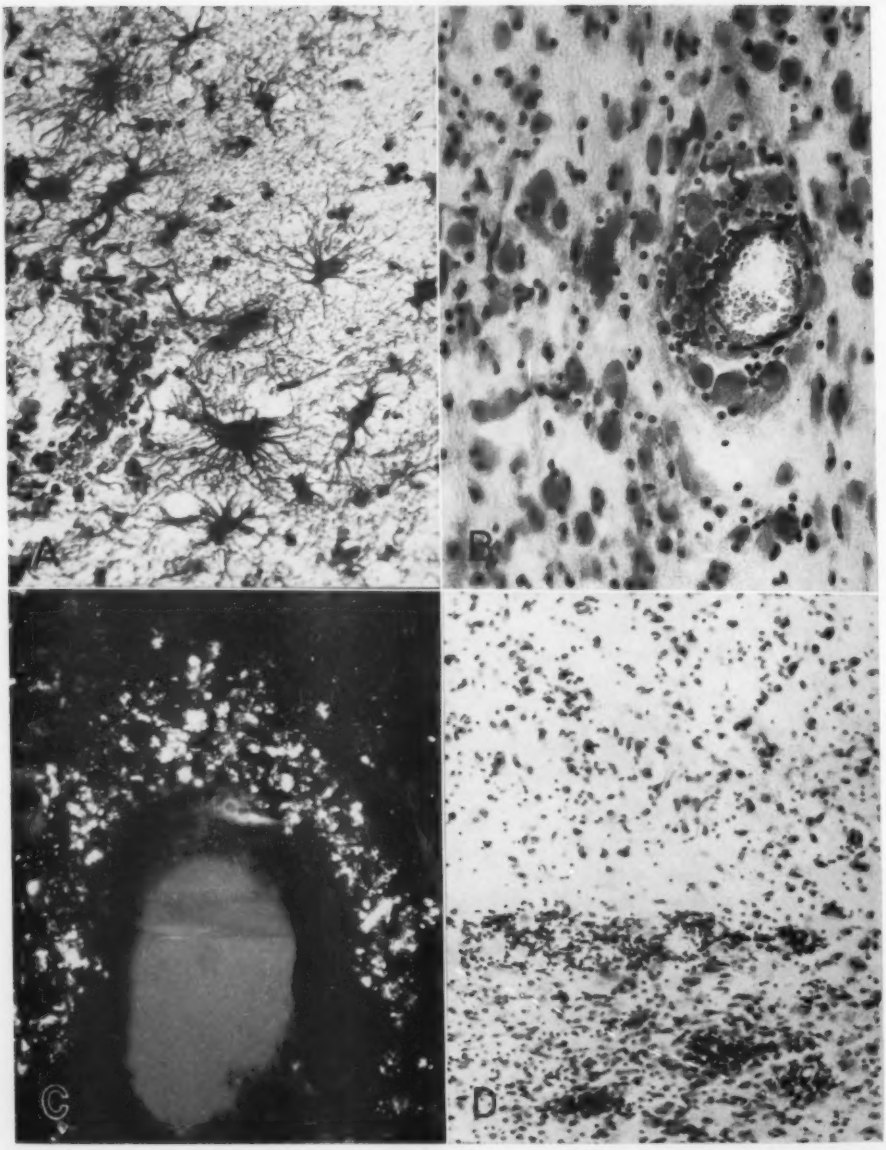

Fig. 3. [A] Reactive astrocytes in the demyelinated white matter. Heidenhain. × 400. [B] Border of the demyelinated region showing lymphocytes and macrophages. PAS. × 400. [C] A blood vessel from the border of the demyelinated region showing birefringence of macrophages. Sudan red—PAS. × 500. [D] Border between the cortex (upper half) and an area of demyelinization with severe inflammatory response (lower half). Cresyl violet. × 200

to ganglioside by using the formula given by Klenk.[8]

The results are recorded in Table 2, from which it will be seen that the normal areas of white matter and cortex gave figures for the various substances that are substantially normal, apart from a very slight loss of phospholipids and a slight increase of ganglioside in the cortex.

The demyelinated areas showed very severe loss of phospholipid, cholesterol, and cerebroside, with an increased water content. The hexosamine level was raised to a figure well above normal. The kidney tissue also showed some increase in hexosamine.

As a result of the findings of a loss of phospholipid, an absence of cholesterol ester, and a raised hexosamine content in the affected white matter, a diagnosis of metachromatic leukodystrophy was considered probable. This suggestion was at variance with the histologic findings. Accordingly, a fresh portion of brain for examination was taken from an area in close proximity to the U fibers, where sudanophilic material was shown histologically to be present; the chemical results are shown in Table 2.

It will be seen that there is a loss of phospholipid and cholesterol similar to that found before but that there is also a considerable amount of esterified cholesterol present. These findings are compatible with a diagnosis of sudanophilic diffuse sclerosis, which is in accord with the histologic views, even though the hexosamine level is raised.

Despite the fact that the normal cerebral white matter of our patient showed a hexosamine content that was within normal limits, we wanted to perform another control estimation on material fixed by embalming fluid. A piece of brain was obtained from a body fixed in a manner identical to that used in our case. The chemical analysis of this nervous tissue showed the hexosamine content to be within normal limits.

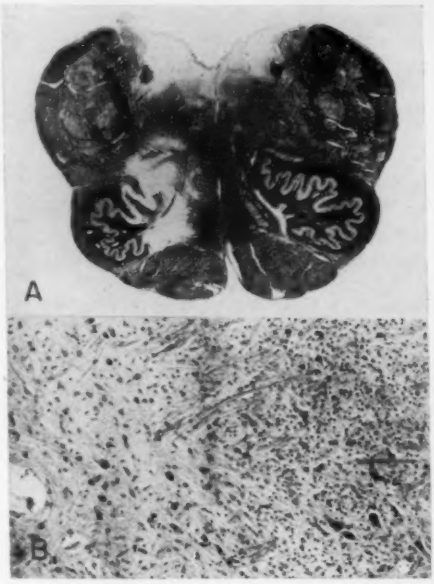

Fig. 4. [A] Transverse section through medulla showing demyelinization in the region of the inferior olive and adjacent to the floor of the fourth ventricle on the left side. Note the asymmetry of myelinization around the solitary tract and hypoglossal nucleus. There is also a slight decrease in myelin density in the medial longitudinal bundle and tectospinal tract on the left side. [B] Border of demyelinated area in medulla. The left side of the picture is the demyelinated plaque. On the right side, there is a slight increase in small round cells. Hematoxylin-eosin. × 200

DISCUSSION

Cases of diffuse demyelinating cerebral sclerosis have been divided on the basis of histologic characteristics and chemical alterations of the involved white matter. This case demonstrates that neither of these methods may be entirely satisfactory unless they are correlated and one remembers to view the chemical results in their entirety.

Examination of the involved white matter in this case showed the presence of sudanophilic material and absence of metachromasia. In addition to our own histologic observations, portions of abnormal white matter were reviewed by two other independent neuropathologists, who agreed that no metachromatic material was present. (We gratefully acknowledge Dr. L. Roizin and Professor W. Blackwood's help in evaluating this material.) On the other hand, chemical investigations at first showed an increased amount of hexosamine and an absence of cholesterol ester, findings

TABLE 2

LIPID CONTENT OF BRAIN OF PATIENT AND NORMAL BRAIN

	Patient				Normal brain†	
	Cerebral white			Cerebral cortex		
	Normal area	Demyelinated area	Area close to U fibers	Normal area	Cerebral white	Cerebral cortex
Total phospholipid	21.7* (6.4)**	4.0 (0.33)	6.0 (0.5)	17.2 (2.19)	(6.2 — 9.3)	(3.1 — 4.6)
Sphingomyelin	10.0 (3.0)	1.4 (0.12)	2.3 (0.2)	5.7 (0.7)	(1.8 — 4.3)	(0.3 — 0.9)
Total cholesterol	13.8 (4.1)	2.6 (0.22)	18.8 (1.56)	7.3 (0.9)	(3.6 — 5.4)	(0.6 — 1.4)
Esterified cholesterol	0.4 (0.13)	0.4 (0.03)	9.6 (0.76)	0.4 (0.05)	0	0
Cerebroside	20.1 (5.9)	1.2 (0.1)		10.1 (1.3)	(4.1 — 7.4)	(0.3 — 1.9)
Ganglioside				1.6	0.1 — 0.2	0.9 — 1.1
Total hexosamine	0.26	0.62			0.24	0.46
Water	70.6%	91.7%	91.8%	87.3%	67 — 74%	81 — 87%

*Results in grams per 100 gm. of dry tissue.
**Figures in brackets indicate grams per 100 gm. of fresh tissue.
†Normal figures taken from Rossiter,[9] Cumings,[2,10] and Cumings, Goodwin, and Curzon."

that are common in cases of metachromatic leukodystrophy. However, since sudanophilic and birefringent material was found at the border of the demyelinated region in histologic sections, special search for cholesterol esters was made. And, indeed, when small pieces of tissue from the advancing border of the lesions were analyzed chemically, cholesterol esters were then found.

From these observations, some conclusions and lessons may be learned. The histologic and biochemical examination of the large demyelinated areas revealed that different stages of myelin breakdown or gliosis may be present in different regions. Therefore, the biochemical investigation of one selected site may not be representative of the whole lesion, whereas, conversely, an analysis of the total abnormal material may not reflect the local arrangement. It is therefore necessary that more than one area of demyelinated tissue be examined and that the portions so taken should, if possible, be obtained with the help of a histologist, who may, in certain cases, know the area of choice. Another point of importance, which may not depend upon the choice of the piece of tissue, is that an error of interpretation may be due, as in this case, to placing emphasis upon one single feature, here the increase of hexosamine, without proper consideration of the findings as a whole. In our experience, such a gross loss of phospholipids and cholesterol has never been found in metachromatic leukodystrophy; consideration of this point should have prevented the first opinion being given as a result of the chemical analysis, but knowledge is obtained only by wide experience. Only old lesions of gliosis resulting from either sudanophilic diffuse sclerosis or multiple sclerosis show such a gross loss of all the myelin lipids without the presence of cholesterol esters, and, in both these conditions, the ganglioside and hexosamine levels may be raised in the cortex and white matter, respectively. In one other case of sudanophilic diffuse sclerosis which one of us has seen, the level of hexosamine was as high as it was in the case described here. Tingey[12] has recently reported raised levels of hexosamine in conditions other than metachromatic leukodystrophy, and Cumings[13] has recently described 7 cases of subacute leukoencephalitis of the van Bogaert, or inclusion body, type, in which the hexosamine level in the cerebral white matter was also increased. It is clear, then, that, in varying types of demyelinization, there may in fact be a raised level of hexosamine even in the absence of cholesterol ester. Whether this represents one form of demyelinization or whether it occurs at a specific time in the actual progress of demyelinization is not at present known.

Another relevant aspect of this case was the finding of lesions in the brain stem which were indistinguishable from the plaques of multiple sclerosis. We do not think that the presence of these lesions in the brain stem and the histologically different areas of demyelinization in the cerebral hemispheres were coincidental and unrelated. Thus, it is possible that these two lesions represent different stages of the same process. In the brain stem, the process became self-limited and burnt out, whereas, in the cerebral hemisphere, it was still actively advancing. This raises the question of the relationship of this case to typical multiple sclerosis, but, because of our still complete ignorance regarding the etiology and pathogenesis of this disease, we would prefer to refrain from any speculations on this subject.

SUMMARY

A 44-year-old man had a progressive disease of seven years' duration which consisted of increasing pyramidal signs, mental deterioration, and, finally, blindness.

Pathologic changes consisted of large, symmetric areas of demyelinization in the parieto-occipital lobes with accumulation of PAS-positive material throughout the lesion and sudanophilic material at its border. In addition, plaques like those of multiple sclerosis were seen in the brain stem.

Quantitative chemical analysis showed an increased hexosamine content throughout the lesions in the cerebral hemisphere, with increased cholesterol esters at the border only.

This case points out that the increased hexosamine content is not necessarily correlated with metachromatic leukoencephalopathy. In addition, when large areas are chemically analyzed, selection of the tissue influences the results considerably and should be conducted with the histologic appearance in mind. Due consideration of the chemical findings as a whole and not of a single feature is essential.

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Treatment of malignant brain tumors with alkylating agents

Thio-TEPA (triethylene thiophosphoramide): Its differential concentration and toxicity after arterial infusion

Vernon H. Mark, M.D., Raymond N. Kjellberg, M.D., Robert G. Ojemann, M.D., and Albert H. Soloway, Ph.D.

THE POSSIBILITY of successfully treating brain tumors with chemical and physical agents delivered to the area of neoplasm by direct carotid or vertebral artery infusion is being investigated by our group. Two biologic factors favor this possibility. First, the overwhelming majority of primary brain tumors do not metastasize to other organs of the body. Second, the unique blood-brain barrier mechanism of the central nervous system is altered locally by neoplastic tissue. Substances introduced into the systemic circulation enter tumor tissue at different rates and concentrations as compared with normal brain.[1,2] The chance that alkylating agents or antimetabolites might penetrate this barrier to a much higher degree in tumor tissue and consequently destroy or inhibit the neoplasm without altering the function of normal cerebral substance has stimulated this investigation. It was further hoped that delivery of the agent via the arterial route would limit a higher proportion of the whole dose to the zone irrigated by the infused artery.

The literature on the subject of patients with brain tumors treated with chemotherapeutic agents is meager. In 1952, French and associates[3] reported the use of intracarotid nitrogen mustard in cats, monkeys, and 3 human beings, 2 with metastatic tumor and 1 with oligodendroglioma; 1 patient with metastatic tumor did show a marked clinical improvement after initial therapy.

Bateman[4] injected thio-TEPA transcutaneously into the area of a gliomatous tumor and also gave this drug intravenously; 2 patients received the drug by both of these routes with equivocal results. A patient with a clinical diagnosis of glioma of the pons was treated with intravenous thio-TEPA; it was reported that he improved over a three-month period and then gradually failed. No central nervous system toxic effects were noted.

Mark and Hall[5] injected thio-TEPA directly into a glioblastoma during craniotomy. The injections were made in tumor areas that selectively concentrated ionic radioactive phosphorus (P^{32}) as tested with the Robinson type of Geiger-Müller probe counter. A dramatic decrease in intracranial pressure without significant change in neurologic status was noted in 2 of 4 patients two weeks after the injection. Air studies done in 1 of these patients showed a shift of the ventricular system toward the side of the tumor. However, postmortem findings five months later were confusing, since glioblastoma invading the opposite side may have been responsible for the ventricular shift. Kjellberg and Ojemann[6] have studied the effect of the intracarotid injection of nitrogen mustard in cat and man. Cats given a maximum dose of 0.4 mg. of nitrogen mustard per kilogram of body weight showed no neurologic

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abnormality. No clinical or toxic effects were observed when 0.3 mg. per kilogram was injected into the carotid artery of a patient with glioblastoma of the dominant frontal lobe.

Davis, Shumway, and Siu[7] injected thio-TEPA into the carotid artery of 8 patients with clinical diagnoses of metastatic tumor of the brain. In the 1 case history reported, the drug was not toxic and striking improvement in the patient's condition was noted. In addition, Krementz, Kokama, and Llewellyn[8] found thio-TEPA to be most effective, as measured by the inhibition or regression of glioma growth in tumor transplants in the anterior chamber of the guinea pig's eye.

Austin and Roth[9] have developed a method of prolonged carotid infusion of alkylating agents and other cancerocidal drugs into the vascular bed of brain tumors.

METHODS

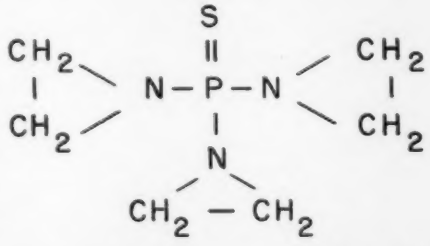
In 5 patients with presumptive diagnoses of glioblastoma multiforme, craniotomy or craniectomy opening was carried out and the tumor exposed. In any instance in which tumor was not apparent on the surface, corticectomy was made and gross tumor visualized. Care was taken to minimize destruction of the blood supply to the zone of study; 2 Robinson-type Geiger-Müller probes connected to scalers were fixed in position by skull-supported clamps, 1 probe tip in the tumor and the other in normal cerebral tissue in the zone irrigated by the appropriate carotid artery. The ipsilateral internal carotid artery was isolated in the neck. The radioactive agents were then injected over a two- to three-second period, and continuous simultaneous probe counting was begun. Cumulative counts were noted beginning at zero time. Initially, counts were recorded every ten to fifteen seconds for one to two minutes; then thirty-second intervals were counted for five minutes. Later, one- to five-minute intervals were recorded. Count-per-minute rates were later computed for each agent. Tumor versus normal ratios could then be compared.

Thio-TEPA labeled with P^{32} was infused in doses of 30 to 80 mg. containing 100 or 200 μc. of P^{32}. After count rates had been stable for at least five minutes, a comparable 100- to 200-μc. administration of ionic P^{32} was injected and recorded in the same fashion. Count rates determined for ionic P^{32} were corrected for the residual counts remaining from the labeled thio-TEPA P^{32}.

In 1 case (A.B.), the ionic P^{32} was given initially, followed by the thio-TEPA injection labeled with P^{32}. Another patient received, in addition, 100 μc. of radioactive rubidium (Rb^{86}) with determinations made in the same manner. Another patient was given unlabeled thio-TEPA via the vertebral artery for treatment of a pontine glioma diagnosed by pneumography.

SYNTHESIS OF P^{32} THIO-TEPA

A solution of 20.7 cc. of triethylamine and 7.7 cc. of ethylenimine in 100 cc. of anhydrous toluene was cooled to 0° C. in a 3-neck flask equipped with a stirrer, a dropping funnel, and a condenser through which a thermometer



was inserted into the reaction media. In the dropping funnel was placed a solution of 50 cc. of (toluene) anhydrous toluene containing 5 cc. of P^{32} thiophospheryl chloride (1 cc. of $P^{32}SCl_3$ containing 15.6 mc. per cubic centimeter was diluted with 4 cc. of nonradioactive thiophospheryl chloride). The thiophospheryl chloride solution was added with stirring at such a rate that the temperature did not rise above 5° C. throughout the entire reaction. After the addition, the solution was stirred for an additional thirty minutes, and the precipitated triethylamine hydrochloride was then filtered off. The toluene solution was concentrated to dryness under a vacuum, and the oily solid residue was recrystallized twice from petroleum ether. A sample of the solid was dissolved in water and filtered through millipore paper into a sterilized capped bottle. The solution was used for injection without further sterilization.

DISTRIBUTION STUDY

The lipid solubility of compounds is one criterion that has some merit in determining the distribution of a substance between brain tumor and brain.[10] A high concentration in a lipid phase results in a higher concentration in the normal brain relative to tumor. By comparing the amounts of a compound distributed between benzene, a lipid solvent, and water, the ratio of relative solubilities or partition coefficient may be determined.

To determine the partition of thio-TEPA, approximately 5 mg. of the radioactive material was distributed between 50 cc. of water and 50 cc. of benzene. The layers were separated, and the counts per minute were determined for each volume by counting at a distance of approximately 5 cm. from the surface of the liquid.

	Counts per minute
Aqueous layer	1,000
Benzene layer	12,000

It would appear that, on this basis, thio-TEPA would be quite lipid-soluble and might concentrate to a greater extent in brain than in brain tumor.

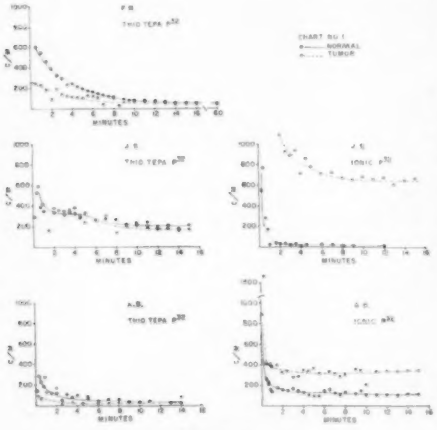


Chart 1

CASE REPORTS AND RESULTS

Case 1. F.N. was a 62-year-old white male. A presumptive diagnosis of glioblastoma involving the right frontal area was made after carotid arteriography. Through a trephine opening, a cortical tumor was exposed in the right frontal lobe. The probe was inserted into the neoplasm and a second probe into the normal parietal area. The right internal carotid artery was isolated in the neck, and 43 mg. of thio-TEPA P^{32} was injected. Counting showed that the tumor-to-brain ratio stabilized at approximately 1 to 1. Biopsy at this initial operation showed grade II astrocytoma (Chart 1).

Charts 1 and 2. Comparison of counts per minute (C/M) recorded at operation on each patient. Note the high tumor-to-brain ratio with ionic P^{32} and the lack of any significant difference in the concentration of thio-TEPA labeled with P^{32}.

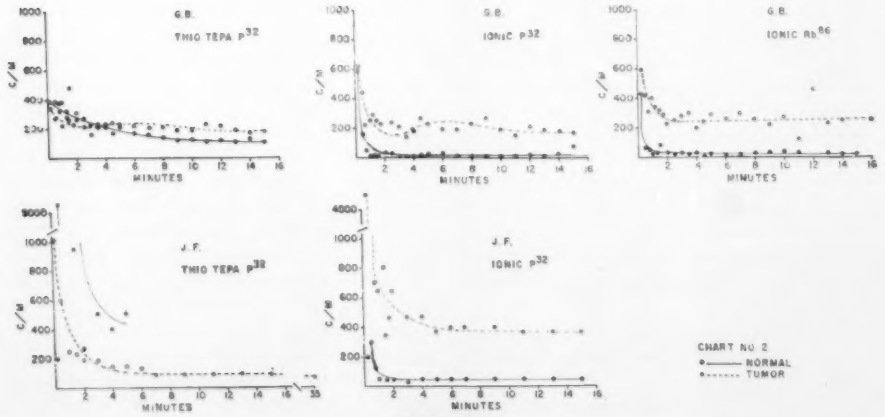


Chart 2

Case 2. J.S. was a 42-year-old white male. A surface tumor that had the gross appearance of a glioblastoma was exposed in the left parietal area. A probe was placed in the tumor and another in the normal left parietal region; 80 mg. of thio-TEPA P^{32} was injected into the isolated left carotid artery. The tumor-to-brain ratio stabilized at approximately 1 to 1. After this, 200 μc. of P^{32} was given by the same route, and tumor-to-brain ratio was 14 to 1. Biopsy showed grade III astrocytoma (Chart 1).

Case 3. A.B. was a 60-year-old woman. A tumor with the characteristics of a glioma was noted in the superficial frontal area on a left carotid arteriogram. Osteoplastic craniotomy exposed the surface neoplasm. A probe was placed into this area and a second probe into the normal posterior temporal region. After the left internal carotid artery was isolated, 100 μc. of P^{32} was given with the tumor-to-brain ratio stabilizing at about 3 to 1. Thio-TEPA P^{32}, 30 mg., was then administered in the same manner, with a resulting tumor-to-brain ratio of about 1 to 1 (Chart 1). Pathologic examination of the biopsy substance showed grade III astrocytoma.

Case 4. G.B. was a 44-year-old white male. Carotid arteriography showed a deep right frontal tumor, the gross appearance of which was consistent with glioblastoma. Right frontal craniotomy was done, and partial resection of the right frontal lobe was carried out, exposing the tumor. A probe was inserted into this area, and a second probe was placed into normal brain in the parietal region. The right internal carotid artery was exposed, and 59 mg. of thio-TEPA P^{32} was given. The tumor-to-brain ratio stabilized at 1.5 to 1. Ionic P^{32}, 100 μc., was given, and a tumor-to-brain ratio of 10-15 to 1 was recorded (Chart 2). Biopsy showed grade III astrocytoma. In addition, this patient was given 100 μc. of Rb^{86} with a tumor-to-brain ratio of 10-15 to 1.

Case 5. J.F. was a 62-year-old white male. Left frontal craniotomy revealed a large surface tumor of the anterior central portion of the left frontal lobe. On gross examination, it was thought that the tumor was probably a glioma. A recording probe was placed in the tumor and another in normal cerebral tissue. The left internal carotid artery was isolated, and 58 mg. of thio-TEPA P^{32} was given, with a resulting tumor-to-brain ratio of 1 to 1. Administration of 100 μc. of ionic P^{32} gave a tumor-to-brain ratio of 10 to 1. Biopsy showed undifferentiated metastatic tumor (Chart 2).

Case 6. S.B., a 6-year-old boy, had a diagnosis of pontine glioma established by clinical and pneumoencephalographic criteria. The left vertebral artery was exposed, and 15 mg. of thio-TEPA was given. One week later, it was noted that, in contrast to his preinjection state, he could eat solid foods and saliva stopped drooling from his mouth. Subsequently, his condition again worsened. The artery was reexposed, and a second dose of 30 mg. of unlabeled thio-TEPA was given. The patient's downhill course continued unabated until his death.

DISCUSSION

After reading and hearing reports of thio-TEPA's therapeutic effect on clinical cases of brain tumor, we were disappointed to find that this agent did not selectively concentrate in malignant cerebral neoplasms. At the present time, of course, it is impossible to assess the importance of concentration studies as a guide to the therapeutic possibilities of a cancerocidal drug. Obviously, if a given agent were extremely toxic to tumor tissue and innocuous to normal brain, the concentration studies would be of minor importance. Unfortunately, such an agent has not yet been found. We are, therefore, in the process of working with water-soluble alkylating agents that promise to concentrate selectively in malignant cerebral neoplasms. Concentration studies are being carried out with these agents and will be reported in the near future.

The biologic properties of cancerocidal agents are of critical importance. However, it is difficult to measure the ability of a given cancerocidal drug to selectively destroy brain tumor cells without altering normal surrounding brain. Even repeated careful neurologic examinations can be misleading. A slight improvement in the patient's clinical course may be interpreted as a beneficial drug effect, whereas it is, in reality, only part of the grossly fluctuating pattern seen in some patients with untreated cerebral neoplasm.

In our opinion, reduction in tumor size, as determined by measured comparisons of pre- and posttreatment arteriograms or air studies, is the most reliable index of the given agent's cancerocidal activity. This would be particularly true if the functions of the injected hemisphere were maintained or improved.

The patients treated in this series had surgical removal of their tumors after injection and counting of the labeled agents. It was impossible, therefore, to ascribe changes in tumor size or neurologic status to the injection of alkylating agents per se. We are now in the process of evaluating patients with recurrent tumors treated only with intracarotid injections

of cancerocidal agents or injections combined with bilateral carotid perfusion technics utilizing the pump oxygenator. (This work is being done in collaboration with Drs. W. Sweet, J. Raker, R. Shaw, and G. Austin.)

We were concerned about the possible toxic effects of thio-TEPA injections into the carotid or vertebral circulation. In the 6 patients reported in this study, no signs or symptoms of clinical worsening were seen in the immediate postinjection period. Bone marrow depression was also absent in spite of the relatively large dose of drug injected into the cerebral circulation.

CONCLUSIONS

1. The concentration rate of arterially infused thio-TEPA labeled with P^{32} has been determined in malignant brain tumors as contrasted with surrounding normal brain in patients. This agent does not preferentially concentrate in malignant brain tumors which do selectively concentrate ionic P^{32}.

2. Administration by carotid perfusion of thio-TEPA in the doses noted did not produce signs of toxicity in the central nervous system or bone marrow.

3. The high lipid solubility of thio-TEPA correlates with its lack of selective concentration in brain tumors as contrasted with normal brain.

4. No attempt was made to ascribe clinical improvement to thio-TEPA injection because of subsequent surgical therapeutic measures. Criteria for future evaluation of biologic effects are outlined.

ADDENDUM

Dr. Barnes Woodhall and associates have had extensive experience with the cranial perfusion of alkylating agents. Their recent publication emphasizes the effect of hyperthermia upon cancer chemotherapy.[11] They are also carrying out tracer studies by injecting alkylating agents tagged with P^{32} into the carotid circulation.[12]

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Usefulness of photic stimulation in routine clinical electroencephalography

John R. Hughes, M.A. (Oxon.), Ph.D., with the technical assistance of M. J. Curtin, A.B., and V. P. Brown

VARIOUS STUDIES have dealt with different types of abnormal responses to photic stimulation in clinical electroencephalography. These studies have frequently featured epileptiform responses and depressed photic responses but have usually involved a special type of patient population. However, the usefulness of photic stimulation in routine clinical electroencephalography remains a question. This study was done to answer this practical question, often posed by us who use the procedure and by others who are willing to be convinced that they should incorporate photic stimulation as a routine procedure in clinical electroencephalography.

APPARATUS AND METHODS

Routine clinical electroencephalograms were made on 1,326 patients with the use of the 10-20 International System of electrode placement (collodion) on an 8-channel (Model III D) Grass electroencephalograph. For the purposes of this study, only the first record for each patient was considered. The patient population was fairly general because Meyer Memorial Hospital is a county institution. Photic stimulation was employed as part of the examination of each patient. A stroboscopic bulb of a Buffington photic stimulator was placed directly in front of the patient, approximately 8 in. from the eyes. Both the patient's room and the recording room were darkened, and various frequencies of stimulation from 1 to 30 per second were used. Each of 12 to 14 different stimulating frequencies within this range was maintained for a duration of ten to fifteen seconds; at times, the frequency of 16 per second was used in a repeating ratio of two seconds on to one second off in search of epileptiform complexes.[1] The last part of the examination with photic stimulation involved a slow decrease in the stimulating frequency from 30 to 1 per second over a twenty- to twenty-five-second period.

In the evaluation of the response to photic stimulation, records were divided into 3 categories: [1] driving, [2] no driving, and [3] epileptiform. The term driving refers to photic responses that have a relationship to the frequency of the photic stimulus and includes harmonic and subharmonic responses. A concerted attempt was made to be conservative about the designation of an epileptiform response and usually only clear, bilaterally synchronous and symmetric spike and wave complexes were so designated (Fig. 1). Photic responses such as slow and sharp paroxysms, frontal sharp transients, and various dysrhythmic responses appear to be questionable in significance and were therefore excluded from the category of clear epileptiform responses.

The records showing driving were divided into those with no significant asymmetry and those with significant asymmetry of photic response. Significant asymmetry was defined as more than a 50% amplitude difference between the photic driving of the 2 hemispheres. Asymmetric responses also include those showing clear harmonics and subharmonics in one hemisphere and not in the other. The records were further subdivided into 4 categories: [1] no driving, [2] poor to fair driving, [3] good driving, and [4] excellent driving (Figs. 2 through 4). This latter classification is, of course, arbitrary. Although the responses to photic stimulation show considerable variabil-

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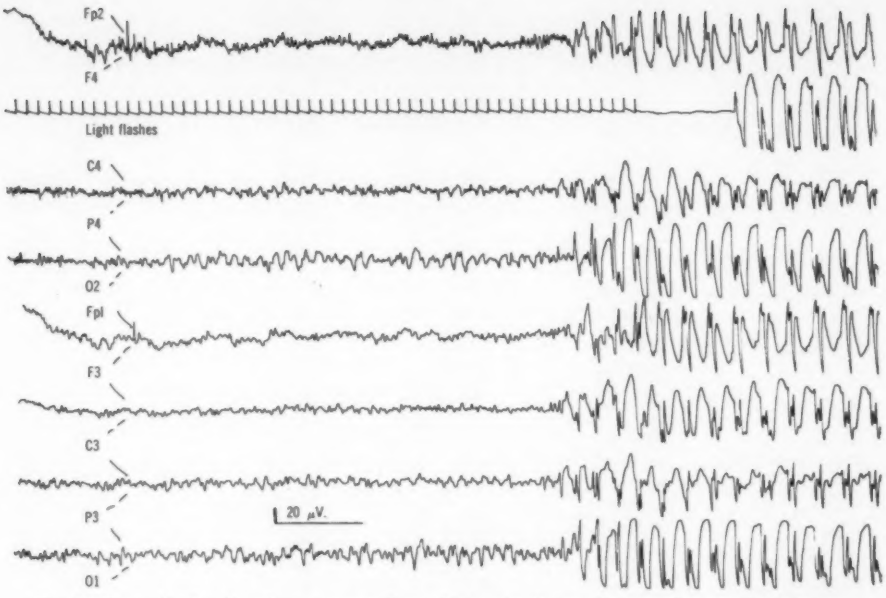

Fig. 1. Example of epileptiform response from photic stimulation. See text for specific definition.

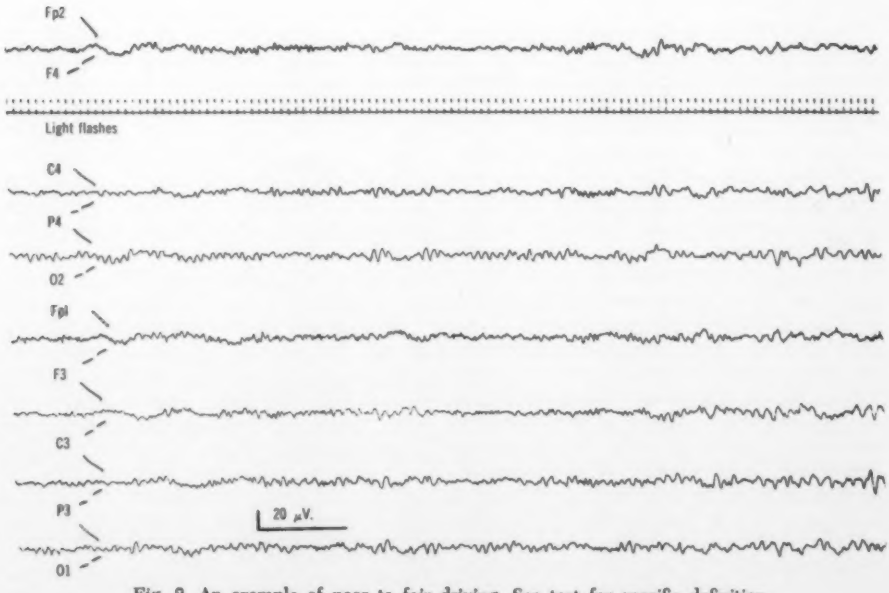

Fig. 2. An example of poor to fair driving. See text for specific definition.

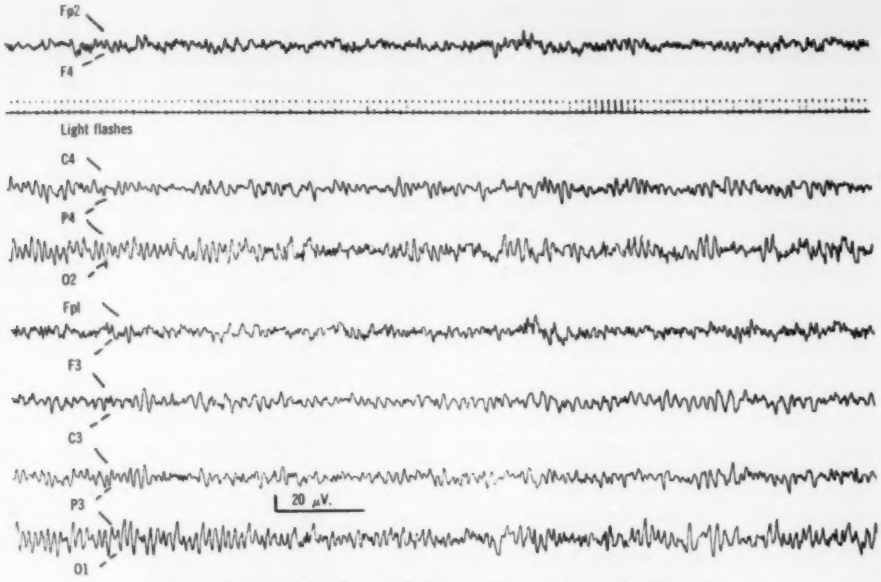

Fig. 3. An example of good driving. See text for specific definition.

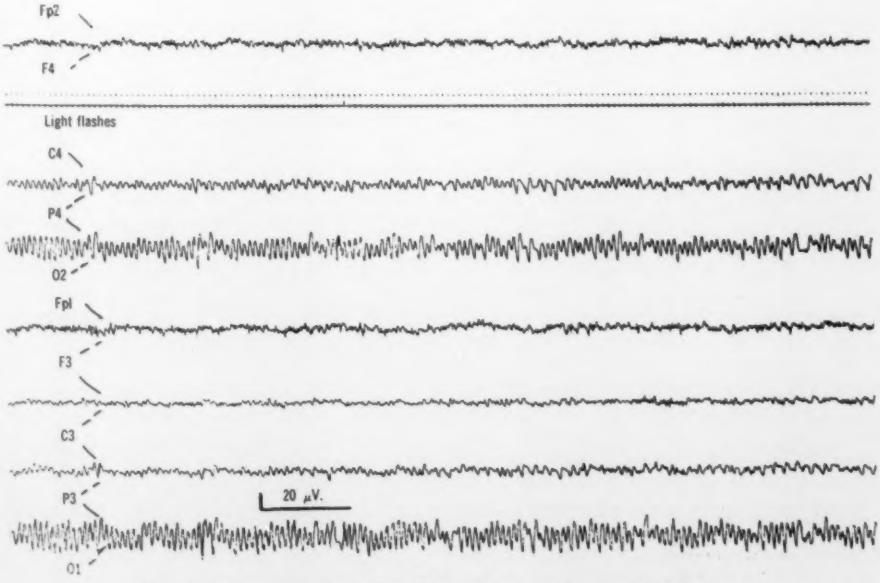

Fig. 4. An example of excellent driving. See text for specific definition.

ity, an attempt was made to follow certain objective criteria in the classification. Incidence of clear photic response within the ten- to fifteen-second period of stimulation served as the major criterion. Excellent driving showed clear photic responses during more than two-thirds of the stimulation period; good driving showed responses during less than two-thirds but more than one-third of the time; and poor to fair driving showed responses during less than one-third of the stimulation period. The amplitude of these responses, seen on the bipolar, anterior-posterior montage, also served as a criterion. Usually, excellent driving showed responses larger than 40 μv., good driving less than 40 μv. but more than 20 μv., and poor to fair driving less than 20 μv. Although some patients showed clear driving with the lower frequencies of stimulation and not with the higher frequencies, stimulating frequencies of 12 to 18 per second proved most useful in evaluating photic driving.

Disregarding the responses to photic stimulation, we then attempted to interpret the records for abnormalities in a conservative manner. Borderline "normal" (10%) and "normal" records (34%) were combined and considered as one group in this study (44% of all records). Abnormal records were divided into those showing [1] unilateral and [2] bilateral abnormalities. Relatively rare midline abnormalities and bilaterally synchronous and symmetric spike and wave complexes were arbitrarily classified as bilateral abnormalities.

Records were evaluated for prominence of beta rhythms, seen maximally on the frontal areas but, at times, diffusely. Records were considered to show prominent beta if these rhythms, especially 15 to 20 per second, exceeded 20 μv. on the frontal areas.

TABLE 1

ELECTROENCEPHALOGRAPHIC ABNORMALITIES AND PHOTIC RESPONSES

	Number of cases	*Per cent of total records*	*Per cent of normal records*	*Per cent of abnormal records*	*Per cent of unilateral abnormalities*	*Per cent of bilateral abnormalities*
All records*	1,326					
Normal	587	44				
No drive	188	15	32			
Drive	399	29	68			
No asymmetry	372	27	63			
Asymmetry	27	2	5			
Abnormal	739	56				
Unilateral	346	26		47		
No drive	114	9		16	33	
Drive	232	17		31	67	
No asymmetry	163	12		22	47	
Asymmetry	69	5		9	20	
Ipsi depressed†	64	5		9	19	
Contra depressed‡	5	0.4		0.7	1	
Bilateral	393	30		53		
Epileptiform	42	3		6		11
No drive	145	11		20		37
Drive	206	16		27		52
No asymmetry	158	12		21		40
Asymmetry	48	4		6		12

*Records are divided into normal and abnormal according to whether a definite abnormality is found in the tracing, excluding photic responses.

†Cases in which a significant depression of photic responses is seen on the side that shows a definite abnormality on the remainder of the record.

‡Cases showing a depression on the side opposite that showing a definite abnormality.
See text for other definitions.

RESULTS

Table 1 shows the results of the study correlating electroencephalographic abnormalities and photic responses. Epileptiform responses are seen in 3% of all cases or 6% of the abnormal cases that show some definite abnormality. In 10 cases (24% of those showing epileptiform complexes), spike and wave complexes were seen mainly during photic stimulation and were only abortive in all other parts of the record, including during five minutes of hyperventilation. One of the more significant findings seen in Table 1 is that 5% of all records or 9% of abnormal records show a significant depression of photic driving in the hemisphere that shows a definite abnormality on the remainder of the record. Only 0.4% of all records or 0.7% of abnormal records show a depression in the hemisphere opposite that showing a definite abnormality. Of the records showing bilateral abnormalities, 12% show a significant depression on one side and contribute evidence as to the side maximally involved. These cases constitute 4% of all tracings and 6% of abnormal tracings.

Table 1 shows that, if all cases of asymmetric driving are considered, 19% show a normal recording in the remainder of the record, excluding the photic responses. If asymmetry of photic responses was striking, the interpretation of a normal record may be somewhat modified to include suggestive evidence for an abnormality in the hemisphere showing depressed driving. Also, of the cases of asymmetric driving, 33% show bilateral abnormalities in the remainder of the record. Asymmetric driving in these cases may aid the electroencephalographer in determining the side maximally involved. Of these cases showing asymmetry of photic driving, the most helpful are probably the 44% that show a depression of driving in the hemisphere that shows an abnormality on the remainder of the record. These cases add a degree of assurance to the electroencephalographer that a given hemisphere is involved. Certainly, the 3% of cases showing asymmetric photic driving with depression in the hemisphere opposite the one showing an abnormality in the remainder of the record offer difficulty in interpretation.

Table 1 reveals the relatively large number of patients (at least one-third) who show no clear photic driving. The symmetry of photic responses can be evaluated only with clear driving; therefore, most of the photic responses were further categorized into the groups seen in Table 2.

Good and excellent driving, seen in 29.4% of all cases, often appear best in records showing prominent (frontal) beta rhythms, especially rhythms of 15 to 20 per second. A statistical analysis of records with prominent beta rhythms shows that these rhythms are seen in almost twice as many records showing good and excellent driving (37%) than records with poor to fair and no driving (19%). Good and excellent driving is seen in 45% of records with prominent beta rhythms; Table 2 shows that good and excellent driving is seen in only 29% of all records.

TABLE 2

CLASSIFICATION OF PHOTIC RESPONSES

	Number of cases	*Per cent of total cases*
No driving	419	33.1
Poor to fair driving	433	34.2
Good driving	274	21.6
Excellent driving	99	7.8
Epileptiform responses	42	3.3
Total	1,267	100.0

See text for definition of terms.

DISCUSSION

Table 1 shows that epileptiform spike and wave complexes, bilaterally synchronous and symmetric, are seen from photic stimulation in 3% of all records and 6% of all abnormal records (those showing a definite abnormality in the remainder of the tracing, excluding the photic activation). These cases provide a significant degree of assurance that a "centrencephalic" type of epileptogenic disorder is involved. The 10 cases showing clear spike and wave complexes only from photic stimulation in a record showing otherwise only abortive complexes exemplify the great value of this type of activation in a certain small proportion of cases. Other studies[2–5] have reported a higher percentage of abnormal responses, but these studies usually involved special types of patient populations, like mentally normal senile per-

sons, persons of deviant behavior with seizures, and children without seizures. The present study was designed to show the percentages of abnormal responses in routine clinical electroencephalography.

A significant depression of photic driving in the same hemisphere that shows a definite abnormality in the remainder of the record is noted in 9% of abnormal cases. Kooi, Eckman, and Thomas[6] have reported that 46% of cases with clinical involvement of one hemisphere and 75% of 8 cases with homonymous hemianopsia show a significant asymmetry. The present study shows that 12% of the cases with bilateral abnormalities have a definite asymmetry of photic responses, while Kooi and associates reported that 23% of cases with bilateral damage showed lateralized responses. The present study incorporates all cases with electrographic abnormalities and is not restricted to cases with surgical or clinical verification, since the emphasis here is to correlate photic responses and electroencephalographic abnormalities.

For proper evaluation of amplitude symmetry, good or excellent driving is desired. The prominence of beta rhythms raises the percentages of this kind of driving from 29 to 45% of records. Mundy-Castle[2] and Gastaut[7] have noted a significant association between the existence of spontaneous beta rhythms and photic driving.

SUMMARY AND CONCLUSIONS

1. Routine clinical electroencephalograms, along with photic stimulation, were made on 1,326 patients.

2. Photic responses were correlated with the findings in the remainder of the record.

3. Of the abnormal records showing some definite abnormality, excluding the photic responses, 6% had clear, bilaterally synchronous and symmetric spike and wave complexes and 9% had a significant depression of driving in the hemisphere in which a definite unilateral abnormality appeared. Thus, results of photic stimulation are helpful in at least 15% of abnormal cases. An additional 6% of abnormal cases, with bilateral abnormalities, show a significant unilateral depression of photic responses and provide evidence for the side maximally involved.

4. Photic responses were further categorized for degree of driving; 33% of all records showed no driving, and 29% showed good or excellent driving.

5. The existence of prominent beta rhythms in the resting record increased the percentage of good and excellent driving from 29 to 45%.

6. The addition of photic stimulation to a routine clinical electroencephalographic examination requires a relatively short amount of time. The information and evidence that this procedure yields seems to argue strongly for its routine use.

The author wishes to thank Dr. Cosimo Ajmone-Marsan for his helpful criticism and Miss Joan Hauser for her aid in the preparation of the manuscript.

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Arachnoidal cyst of the cisterna ambiens

Report of two cases

Akihumi Katagiri, M.D.

ONLY 4 CASES of arachnoidal cyst of the cisterna ambiens have been reported in the literature, 3, in which the symptoms were tumor of the pineal body by Noetzel[1] and 1, in which ventriculographic findings resembled those seen with tumor of the quadrigeminal plate, by Hoshino.[2]

I am reporting here 2 cases of arachnoidal cyst of the cisterna ambiens. The first case was initially clinically diagnosed as parasellar tumor; later, pneumoventriculography indicated arachnoidal cyst of the cisterna ambiens, which was confirmed by postmortem examination. The second case was diagnosed correctly on the clinical findings and treated by ventricular tapping.

Fig. 1. Roentgenogram of skull showing atrophy of the posterior clinoid process

CASE REPORTS

Case 1. K.H. was a 37-year-old woman. Her family history was not pertinent. The patient had nephritis at 16 years of age. In December 1956, she visited a doctor because of headache; examination revealed albuminuria, which was relieved after a month of treatment.

Early in 1957, the patient began to have bouts of sudden frontal headache accompanied by nausea and vomiting lasting a week and gradually passing off in the course of a few days. In April, she noted a slight vertigo and pressure feeling in the right eye. One month later, she lost vision in the right eye, and, in June, the left eye gradually became blind.

The left upper extremity became weak in May; about the same time, generalized convulsions, which lasted ten to twenty seconds, began to occur about once a week. In June, the patient had her last menstrual period. She was admitted to hospital on August 14 with the chief complaints of headache and loss of visual acuity.

Examination. The patient was an average-sized, well-nourished woman with a normal facial expression. Her heart, lungs, and abdomen were normal. Slight anemia was noted. The sedimentation rate was 40 mm. in one hour 55 mm. in two hours.

On neurologic examination, the patient was observed to have generalized convulsive seizures accompanied by unconsciousness and followed by frontal headache. Her memory was impaired. Olfactory sensation was decreased bilaterally. Marked papilledema was present in both eyes. Visual acuity was nil, and the dilated pupils did not react to light or in accommodation. External ocular movements were normal except for fixation and positional nystagmus to the right. The patient complained of tinnitus in the left ear and had mild perceptive deafness bilaterally. The vestibular reactions on both sides were hypersensitive. The superficial and deep reflexes were normal, and no pathologic reflexes were found.

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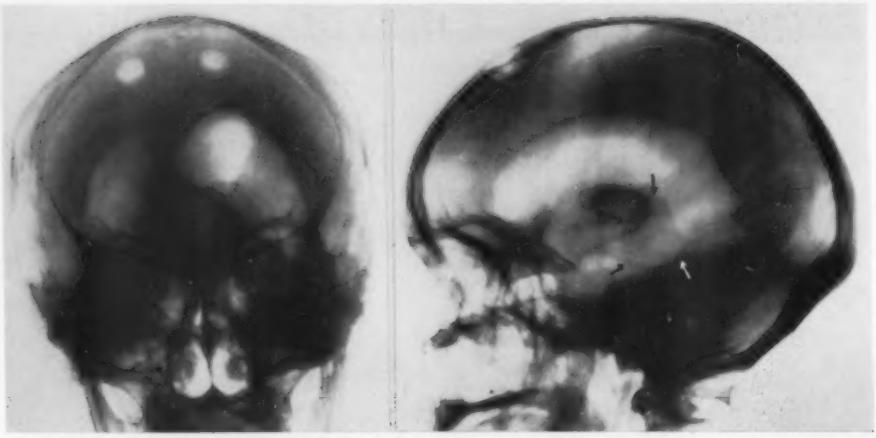

Fig. 2. [A] Face-down ventriculogram showingsymmetric dilation of lateral ventricles, dilated third ventricle, and rounded shadow indenting the floor and medial aspect of the right trigone. [B] Lateral ventriculogram showing walnut-size shadow which anteriorly compresses the third ventricle, inferiorly the aqueduct of Sylvius, and posteroinferiorly the cerebellum and which is superimposed upon the trigone, as indicated by the arrows

Roentgenograms of the skull revealed atrophy of the posterior clinoids and marked diploic channels (Fig. 1).

Slow waves were present in the resting electroencephalogram, but no localized abnormal findings were seen.

In short, there were symptoms of increased intracranial pressure without localizing signs. A parasellar tumor was suspected on the basis of the sellar changes and blindness. Carotid arteriography performed on August 20 was negative. Six days later, a pneumoventriculogram was made, which revealed enlarged and communicating lateral ventricles and dilation of the anterior portion of the third ventricle. A walnut-sized, smooth-margined shadow encroached anteriorly on the third ventricle, inferiorly on the aqueduct of Sylvius, and posteroinferiorly on the cerebellum and posterosuperiorly was superimposed on the shadow of the dilated lateral ventricles (Fig. 2). A tumor of the pineal body could be excluded because of the nature of the shadow, the size of the tumor, the presence of the recessus suprapinealis, and the absence of the characteristic eye symptoms. This roentgenographic picture should have suggested arachnoidal cyst of the cisterna ambiens.

Craniotomy by the pineal approach of Dandy was done with the patient under local anesthesia. Respiratory arrest accompanied by cardiac arrest occurred during the operation. In spite of oxygen administered through an endotracheal tube and intracardiac injection of epinephrine, voluntary respiration did not return and the patient died twelve hours later.

Postmortem findings. Macroscopically, the arachnoid was mildly congested. The cerebral gyri were flattened. The cisterna ambiens formed a hen-egg–sized arachnoid cyst, which communicated through a small hole with the posterosuperior portion of the third ventricle (Fig. 3). The lateral and third ventricles were dilated moderately. The aqueduct of Sylvius was depressed and compressed by the cyst. The fourth ventricle was normal. The medial temporal structures and cerebellar tonsils were herniated. Histologic examination revealed that the wall of cyst consisted of a few layers of arachnoid. No inflammatory reaction was found in the arachnoid, pia mater, or ependyma of the aqueduct of Sylvius. The cellular elements of the cerebellar folia seemed to have pericellular edema. No other remarkable changes in the brain were noted.

Case 2. S.Y. was a 20-year-old man. His

family history was not relevant. He had had no noteworthy disease except chronic maxillary sinusitis.

In December 1946, the patient began to have frontal headache with frequent projectile vomiting. In February 1947, he noted blurring of vision, narrowing of the visual fields, bilateral tinnitus, and vertigo, which was followed several days later by unsteadiness of gait. The patient was admitted to hospital on April 4, because of headache and visual disturbance.

Examination. The patient was an average-sized, moderately well-nourished man appearing to be in pain. His heart, lungs, and abdomen were normal. The sedimentation rate was 3 mm. in one hour and 13 mm. in two hours.

On neurologic examination, the patient had bilateral diminution of olfaction. On cephalic percussion, a cracked-pot sound was audible. Moderate papilledema was present bilaterally. The visual acuity was 2/20 in the right eye and 8/100 in the left. The visual fields were constricted concentrically. The pupillary reaction to light and accommodation was slow but present on both sides. A mild bilateral paralysis of conjugate upward gaze was noted. He had painful paresthesias on the right half of the face. A perceptive type of deafness was present bilaterally. The vestibular function was diminished on the right side, and the patient was unsteady in the Romberg position.

The superficial reflexes were normal, but the achilles and patellar tendon reflexes were abolished bilaterally. No pathologic reflexes were observed.

The dorsum sellae was markedly decalcified in skull roentgenograms. Pneumo- and oleoventriculograms made on April 14 revealed that the lateral ventricles were dilated symmetrically and the third ventricle was enlarged. A shadow defect was seen below the recessus suprapinealis in the posterior portion of the third ventricle. The rostral part of the aqueduct of Sylvius was seen in the ventriculogram, but the fourth ventricle was not visible (Fig. 4).

A shadow suggesting a tumor displacing the posteroinferior portion of the third ventricle forward and the aqueduct downward was observed. There was some doubt that this shadow was caused by a tumor of the pineal body or the quadrigeminal colliculus because there were no other suggestive signs, such as the sluggishness of the pupil, except mild paralysis of conjugate upward gaze. The diagnosis made was arachnoidal cyst of the cisterna ambiens. Ventricular taps were made.

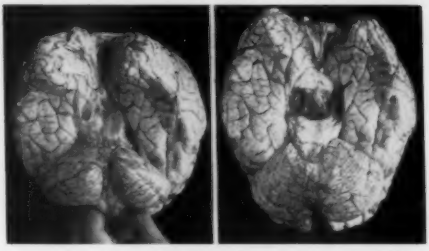

Fig. 3. *(Case 1)* Inferior surface of the brain showing egg-size arachnoidal cyst of cisterna ambiens (arrows)

The headache, olfactory disturbance, and facial paresthesia were relieved by the ventricular tap. Hearing improved so that the patient could hear a normal conversation. The choked disk and paralysis of conjugate gaze receded. Vision in the left eye decreased, so that the patient could hardly appreciate light, but vision in the right eye improved markedly. The patient was discharged on June 3, 1947.

Fig. 4. *(Case 2)* Lateral iodoventriculogram showing a defect of the suprapineal recess and a depression of and obstruction to the rostral part of the aqueduct of Sylvius

He has been working regularly in furniture manufacturing for the last twelve years.

This case resembled the clinical course of a pineal tumor. The facts that the symptoms were relieved by ventricular taps and that the patient has been well for the last twelve years suggest that he did not have a tumor. The sudden change in intracranial pressure induced by ventricular puncture or the drainage of the cerebral fluid may have caused the arachnoidal cyst to rupture. The relief of symptoms might have been due to the restoration of the normal circulation of the ventricular fluid and/or the disappearance of the cyst.

DISCUSSION

Cystic arachnoidal collection of fluid which may be a sequelae of arachnoiditis is one of the conditions included in the category of the so-called "pseudotumor cerebri." The occurrence of pseudotumor cerebri compared with that of brain tumor is 1:43 according to Cushing,[3] 1:40 according to Frazier,[4] and 1:4 according to the statistics of our department.[5] However, arachnoidal cysts of the cisterna ambiens are a very rare form of pseudotumor. The etiology of this cyst is unknown. Possible factors are trauma, allergic reaction, and infection. The 3 patients reported by Noetzel[1] and the second reported here had preceding inflammatory diseases such as maxillary sinusitis. In the present Case 1, the cause is unknown but might be related to whatever factors produced the headache and albuminuria some months before the onset of symptoms.

The anatomic location of the cyst explains the similarity of the symptoms produced to those of pineal tumor. The 3 cases reported by Noetzel and the present Case 2 included such symptoms. The fixed, dilated pupil in Case 1 here was probably due to pressure of the cyst on the quadrigeminal colliculus or to the complete loss of vision. The impairment of hearing, disturbances in equilibrium, and amenorrhea suggest compression of neighboring structures by the cyst. It is interesting that a complete Parinaud's syndrome was not present.

Noetzel stated that diagnosis of this disease is extremely difficult on clinical grounds. One factor may be that the disease is so rare that it is not usually suspected. The ventriculogram gives an important lead.

The first case of Noetzel and the 2 cases presented here are very much alike in that there was a tumor shadow in the posterior third ventricle with dilation of the ventricular system cranially. A pineal tumor usually obliterates the recessus suprapinealis. Vague neurologic findings especially referable to the midbrain, despite the size of the tumor, suggest that the brain stem parenchyma is not involved. In the second and third cases of Noetzel, a communication existed between the cyst and the atrial region of the lateral ventricle, so that the cysts were clearly seen on pneumoventriculograms.

No operative procedures were performed on Noetzel's 3 patients, but all died of central respiratory arrest within a day after pneumoventriculography, presumably because of cerebellar herniation. In Noetzel's second case, the spinal fluid was replaced in the ventricle but this did not prevent death.

The cause of death in the first case reported here seems to have been respiratory arrest of central origin due to herniation of the uncus and cerebellar tonsils. Therefore, pneumoventriculography should be performed with extreme care in order to avoid sudden change in intracranial pressure.

SUMMARY AND CONCLUSION

Case reports on 2 patients with arachnoidal cyst of the cisterna ambiens are presented. The first patients disorder was initially diagnosed clinically as parasellar tumor and later, after pneumoventriculography, as arachnoidal cyst of the cisterna ambiens, which was confirmed by postmortem examination. The second cyst was diagnosed by clinical findings and air study and cured by ventricular taps.

This rare condition is difficult to diagnose. However, the combination of neurologic and ventriculographic findings should suggest it. Air study should be done with great care to avoid sudden change in intracranial pressure.

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CASE REPORT

Convulsive seizures as the presenting manifestation of intermittent porphyria

Jonathan D. Wirtschafter, M.D., Fred W. Turner, M.D., and Robert S. Dow, M.D.

IN ACUTE INTERMITTENT PORPHYRIA, abdominal symptoms occur much more frequently than do neurologic symptoms.[1] Therefore, this diagnosis is often not considered when neurologic findings occur in the absence of abdominal symptoms, gross discoloration of the urine, or a family history of the disease. This is the report of a case of acute intermittent porphyria which presented as a recurrent, febrile, convulsive disorder developing into status epilepticus. The resultant therapeutic paradox will also be considered.

REPORT OF CASE

This 16-year-old white girl was admitted to Good Samaritan Hospital in status epilepticus of unknown etiology on February 25, 1959.

Past history was unremarkable except for intermittent backache that was thought to increase in severity when it was demanded that she do her school work or work in the garden. The backache was of sudden onset and would last about a day at a time. Other vague pains were noted but were not serious enough to demand medical attention. She had fallen from a horse and had been rendered unconscious for five minutes. She had some mild headache after this. She had had no operations, and her system review and survey of habits was not unusual.

Family history. Her father, mother, brother, and sister are well. A maternal aunt suffered from convulsive seizures after a fall. No member of the immediate family showed porphyrins in his or her urine, nor were any symptoms suggestive of this disease noted.

Present illness. The first symptom, believed to be a manifestation of her present illness, was the onset of headache and dizziness associated with slight fever. This began on July 8, 1957, about one year and seven months before our first contact with the patient. On the second day of her illness, her temperature rose to 106° F. and she complained of pain in the back and neck. On the fifth day, she felt much improved, but, on the sixth day, she was unable to sit and complained of "hurting all over" and dizziness. She ate little but did not vomit. She was admitted to a hospital in Roseburg on July 11.

Upon admission, she suddenly stared, stated that she was unable to see, reached her hands above her head, and "clawed the air." She then became unconscious for a period of five minutes. On the following morning, she had an episode characterized by turning of the head to the left, staring, complaints of inability to see or hear, and convulsive movements of the left face, arm, and leg, with lesser activity occurring on the right side. She had 3 subsequent seizures during the next two days, each preceded by a ringing in her head for about an hour. It was observed that her white blood count was 2,500, and she was given a blood transfusion. On her third hospital day, she vomited 3 times during the evening. She was then transferred to a hospital in Eugene for five minutes. She had some mild headache being "ill-appearing, toxic, confused and lethargic."

The blood pressure was 102/64, pulse was 60 and regular, respirations were 24 per

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Fig. 1. Ventriculogram, posteroanterior and lateral views. (Courtesy of Dr. Donald Stainsby, Eugene, Ore.)

minute, and temperature was 98.2° F. rectally. The general physical examination revealed a marked malar flush and no evidence of head trauma, cranial bruit, nuchal rigidity, or papilledema. The neurologic examination revealed the following positive findings: moderate bilateral ptosis; marked loss of conjugate upward gaze; failure of the soft palate to elevate on phonation, although there was no regurgitation during attempts to swallow liquids; dysarthria; constant clonic, convulsive movements of the left leg; occasional clonic, convulsive movements of the left arm and face; diminshed muscle strength in all extremities except the left leg, which could not be adequately tested; hypotonicity in all muscles; pain on movement of the neck but no tenderness; absence of gag and abdominal reflexes; and diminution of deep tendon reflexes without asymmetry. Bilateral impairment of coordination was also noted.

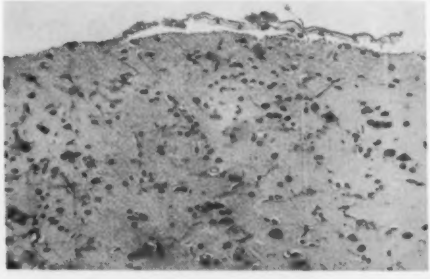

Fig. 2. Brain biopsy removed at the time of the ventriculogram. (Courtesy of Dr. Donald Stainsby, Eugene, Ore.)

A localizing electroencephalogram revealed generalized delta activity with slow (1-2 waves per second) up to intermediate fast waves. Radiologic examination of the skull revealed no definite abnormalities. Lumbar puncture demonstrated an initial pressure of 22 cm. of water. The fluid was clear. No cells were found in the spinal fluid, and the protein and sugar contents were within normal limits. A peripheral blood count was also within normal limits. It was concluded that the patient had a severe encephalitis but that it was necessary to rule out a space-occupying lesion. A ventriculogram was negative (Fig. 1). Biopsy specimens of brain tissue were taken and revealed well differentiated cortical tissue with small areas of acute hemorrhage, probably produced by the biopsy itself (Fig. 2). An apparent glial response with numerous astrocytes in the tissue was noted. There was no evidence of lymphocytic infiltration to suggest an encephalitic process. On July 31, a single urine test for porphyrins was negative.

Because of the frequency of the seizures, the patient was given a general anesthetic of Pentothal on several occasions. However, it was felt that the anesthetic was of no benefit. She was treated with Dilantin, Mysoline, reserpine, Peganone, and Sodium Amytal for her status epilepticus. Nevertheless, the focal convulsions of the left arm and face continued for two and a half months after the onset of her illness, at which time she was transferred to the Oregon State Hospital.

Here her anticonvulsant therapy was continued. It was felt that she exhibited definite psychotic tendencies at times during her hospitalization. Her first sign of recognition of her parents occurred while she was at this hospital. In November 1957, five and a half months after the onset of her illness, she was discharged to her home. For a period of three months, she was free of convulsions, her behavior appeared more normal, and the left-sided paralysis cleared considerably.

In February 1958, she again had left-sided focal seizures for a three-week period, which were not well controlled by Mysoline and Peganone. Her left side became weak but gradually improved, remaining somewhat spas-

tic, yet she was able to ride a horse and walk. In June and September, there were mild episodes of left-sided focal seizures lasting three weeks on each occasion. Between episodes, the patient was a good student and prolific reader.

In January 1959, the patient began to have episodes of seizures which recurred every few days and which had the same left-sided character as those previously described. One week before admission, the patient lost consciousness. She was then hospitalized in Eugene and treated with tetracyline, intravenous Sodium Amytal, Dilantin, and fluids.

She was transferred to Good Samaritan Hospital on February 25 in a comatose state, with almost continuous focal seizures involving the left face and arm and, at times, the left leg. The seizures varied in intensity from one minute to the next. During the seizures, the eyes were held to the left with intermittent nystagmus and, frequently, the head was extended so far as to be opisthotonic. Between seizures, there was no nuchal rigidity. The blood pressure was 138/84; the pulse rate was 92, full, and regular. The general physical examination was unremarkable except for some malar flushing and moderate facial acne.

The neurologic examination differed from that performed one year and six months previously in the following details: no ptosis or paralysis of upward gaze was found; strength, tonus, amplitude, and speed of motion of all extremities had returned to normal except in the left arm, which exhibited mild loss of strength, moderate atrophy, and mild increase in tone; movement of the neck was not painful; the gag and abdominal reflexes had returned; the deep tendon reflexes were normal on the right and moderately increased on the left; the Babinski response was flexor on the right and extensor on the left; and no clonus or tremor was present.

On the third hospital day, partial obstruction of the bronchial tree required tracheotomy. For several days, she was unresponsive, with almost continuous seizures, but, gradually, the convulsive seizures became less severe. An electroencephalogram was performed on the seventh hospital day (Fig. 3) and revealed diffuse, slow, 1.5- to 6-per-second activity of irregular amplitude and frequency. An isolated spike and wave variant pattern

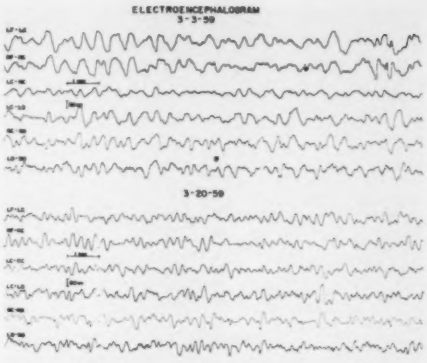

Fig. 3. Electroencephalographic records taken on March 3 and March 20, 1959

was observed in the right frontal region. On the twenty-fourth hospital day, the electroencephalogram was repeated and revealed a significant increase in 4-per-second high voltage activity. In addition, spike and wave variants were evident in the right posterior leads. During this admission, hematologic results were normal except for mild anemia on one occasion and persistent elevation of the sedimentation rate. Routine urinalysis showed some yeast cells, and an initial urinalysis was consistent with dehydration and urinary tract infection. Lumbar puncture findings were consistent with changes due to a traumatic tap on one occasion, and a second spinal puncture revealed a total protein of 62 mg. per cent but was otherwise normal. A moderate decrease in the blood potassium and phosphorus noted at the time of admission was promptly corrected. Prothrombin time, blood urea nitrogen, uric acid, and a battery of liver function tests were all within normal limits. A barium enema and chest roentgenogram were also normal. Skull films and a ventriculogram were not repeated because these had previously been reported normal.

On the eighteenth hospital day, not knowing at the time that a previous urine test for porphyrins had been negative, we raised the possibility of porphyria producing this clinical pattern. The urine porphobilinogen as determined by the Schwartz-Watson test on fresh urine was positive. To more certainly identify

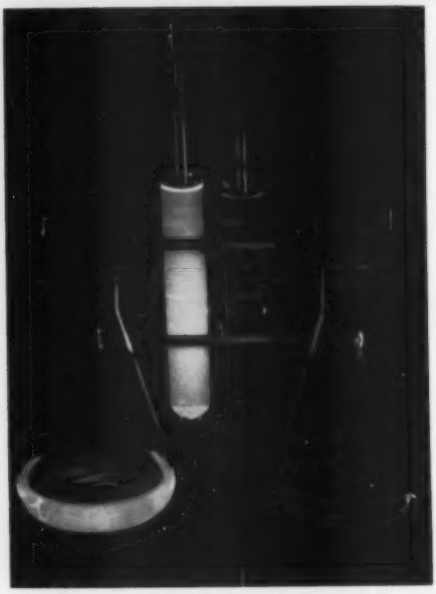

Fig. 4. Positive test for porphyrins in an extract of the urine showing fluorescence under ultraviolet light in the tube and flask to the left and a control extract without fluorescence in the tube and flask to the right

the presence of porphobilinogen, in a typical specimen, the color remaining in the aqueous phase after chloroform extraction was found to show a maximum absorption at 560 μ, which is the characteristic band for porphobilinogen.

In the test for porphyrins, the urine was made acid with a few drops of acetic acid and extracted with ethyl acetate. The ethyl acetate solution was then extracted with 1 N hydrochloric acid. A positive test is indicated by the fluorescense of the hydrochloric acid solution when illuminated with ultraviolet light (Fig. 4). Quantitative anaylsis on a recent twenty-four-hour urine specimen revealed an excretion of 2.8 mg. of uroporphyrin and 1.1 mg. of coproporphyrin.

The initial test was negative, but, subsequently, the urine porphyrins fluctuated frequently between positive and negative, finally becoming regularly positive, while the porphobilinogens were almost always positive from the beginning (see table). The urines of the members of the patient's family were tested and were negative for porphobilinogens on three successive days in all members of her immediate family.

Barbital derivatives, sulfa drugs, and heavy metals were excluded from her therapy. The patient was given 25 mg. of Thorazine three times a day and 100 mg. of Dilantin four times a day. Her seizures did not abate for many weeks. After that time, she improved sufficiently to return home and was discharged on April 5, 1959. She remained there for six weeks, during which time she showed little improvement. She had an average of 1 or 2 left-sided seizures every other day, and these gradually increased in frequency after her discharge. An examination on May 15 demonstrated that she was able to move her left hand and leg but with little control. The platysma and soft palate were without strength, and the pharyngeal muscles were moderately weak. Marked dysarthria was noted. Spasticity and ataxia were evident bilaterally, especially on the left. The deep tendon reflexes were all present but were moderately increased on the left. The Babinski and Chaddock reflexes were positive bilaterally, and the Rossolimo and Oppenheim reflexes were noted only on the left side. Since it was felt that she was again entering into a more acute phase of her disease, she was readmitted to the hospital. She complained of lights darting to the left field of vision. This in turn was associated with the eyes' turning to the left, nystagmus with

RESULTS OF TESTS FOR PORPHYRINS AND PORPHOBILINOGENS

Date	*Porphyrins*	*Porphobilinogens*
March 13, 1959	Negative	Positive
March 15	Negative	
March 16	Positive	
March 25	Slight positive	Positive
April 1	Negative	Negative
April 2	Positive	Positive
April 3	Positive	
May 16	Positive	
May 17	Positive	
May 27	Strong positive	
June 22	Positive	
July 7	Strong positive	
August 11	Positive	
October 16	Positive	

the fast component to the left, head-turning to the left, and, finally, convulsions of the left side of the face, arm, and then leg. The Dilantin and Thorazine therapy was continued. Chloral hydrate was also given.

Endrate Disodium (ethylenediaminetetraacetic acid), 2.5 gm. in 500 cc. of 5% glucose solution, was given intravenously over a four-hour period, once daily for five days. She again required Levin tube feeding and tracheotomy. Her temperature was again elevated from 100 to 102° F. She became lethargic and somnolent.

Subsequent courses of chelating therapy were given on the eleventh, nineteenth, and thirty-seventh hospital days. She became more responsive before the last course was begun and subsequently was able to eat on some occasions without the aid of a nasogastric tube. She was thought to hallucinate some when she was alert. At this time, early optic atrophy was detected. The neurologic examination differed from the previous one in that there was marked hypotonicity in the deep tendon reflexes on the right. The patient was too lethargic to cooperate in voluntary muscle movements.

Continuing superimposed renal infections proved difficult to clear and may have contributed to her febrile state and leukocytosis. After two months' hospitalization, her electroencephalogram revealed an increase in the diffuse slow activity over that observed in her last previous record. At the end of the third month of hospitalization, she had a recurrence of seizure activity when an attempt was made to reduce the dose of Dilantin to less than 4 100-mg. capsules a day. These disappeared when the former dosage was reinstituted. Her neurologic examination at that time revealed an occasional purposeful response to painful stimuli. Her left upper extremity was atrophic and barely movable except at the fingers. The abdominal reflexes were absent.

She was discharged to a nursing home for further care on August 26, 1959. She remains in an essentially vegetative state, responding only to painful stimuli in a semipurposeful way. She is without convulsions on 100 mg. of Dilantin four times a day. Her most recent urine test for porphyrins on October 16 was positive. She moves the right extremities slightly but does not respond to oral command. She does not speak or appear to recognize objects or her relatives. Her eyes have roving movements. She has bilateral positive Babinski reflexes. The left arm and leg show marked atrophy and are completely paralyzed.

DISCUSSION

The classification of porphyria has been the subject of continuing revision and is probably not yet stabilized. The term acute intermittent porphyria is used here to designate those cases described by Waldenström[2] as characterized by the presence of porphobilinogen in the urine during and after attacks and an increase in the urine concentrations of Type III, and to a lesser extent Type I, porphyrins during the attacks.

In brief résumé, this patient had no neurologic or psychiatric symptoms before the present illness except for occasional backaches, headaches, a brief-lived pain in the jaw, and an unremarkable behavior problem. The definite onset of her disease began with fever, headache, dizziness, paralysis, and pain. On the fifth day of her illness, she had the first of innumerable convulsive episodes. On some occasions, these attacks were preceded by a ringing in the head and associated with temporary blindness, deafness, and unconsciousness. There was a widespread and constantly varying pattern of central and peripheral neurologic deficits. The electroencephalogram suggested a diffuse lesion with an epileptogenic focus in the right hemisphere. The convulsive disorder did not respond to Pentothal anesthesia and other anticonvulsant medication. The convulsions disappeared spontaneously after four months, and, after a short phase of psychotic behavior, she suffered for over a year from intermittent periods of left-sided convulsions and fluctuating left-sided weakness. The patient then became unconscious and began to have almost continuous convulsions.

This case of acute intermittent porphyria is presented then as a recurrent, febrile, convulsive disorder. Recently, attention has been drawn to a case of acute intermittent porphyria with convulsions, but this occurred in a woman who had been admitted to a hospital because of epigastric pain.[3] In Waldenström's older series of 103 cases of porphyria, none of

the 7 patients with convulsions was free of abdominal symptoms before the onset of their convulsions. In another series,[4] 10 out of 47 patients had convulsive seizures, and, in 1 (Case 2), severe convulsions were as prominent in the clinical picture as in that of our own patient.

Fever, increased basal metabolic rate, tachycardia, and hypertension have all been reported in porphyria. Thus, a recurrent fever of unknown origin could have its basis in porphyria. In the present case, the inability to control the fever with antibiotics coupled with the neurologic findings caused the process to be considered a viral encephalitis even in the absence of suggestive evidence in the spinal fluid or brain biopsy. Encephalitis without convulsions has occasionally been the initial diagnosis in acute intermittent porphyria.[5]

The patient had a rapid, centrifugal monoplegia with atrophy of the left upper extremity during the second year of her illness. It has been noted that the speed of atrophy in porphyria is more suggestive of poliomyelitis than of a typical polyneuritis. The mechanism may involve a metabolic disturbance in the muscles as well as lesions in the peripheral nerves and anterior horn cells.[1]

The variability of the neurologic findings from day to day would suggest a toxic rather than a destructive organic process. Variability was the keynote of the mental symptoms as well. Alternately, there were periods of unconsciousness, psychosis with hallucinations, and normal, intelligent behavior.

The therapy of status epilepticus due to acute intermittent porphyria is a paradox. Barbital derivatives, sulfa drugs, heavy metals, and alcohol may aggravate the condition. In this case, Dilantin provided some measure of control for the convulsive attacks. It may be that the use of Sodium Amytal, Pentothal, and phenobarbital before the diagnosis was established may have in fact aggravated her condition. It is significant that these agents proved completely ineffective in controlling the seizures.

The use of chlorpromazine has been advocated for the control of pain and other neuropsychiatric symptoms in acute intermittent porphyria.[6] This has been of only questionable value in other reported cases[7] and in the management of this patient.

The role of chelating agents in aiding porphyrin excretion by the removal of zinc and copper has been reported to be helpful in many cases.[4] The patient discussed here received 4 courses of this therapy without a definite association between the therapy and changes in her condition.

In the absence of an effective, specific therapeutic agent for the control of acute intermittent porphyria, therapy has remained symptomatic and supportive.

SUMMARY

1. A case of acute intermittent porphyria is reported. The disease presented as a recurrent, febrile, convulsive disorder without abdominal symptoms.

2. The status epilepticus did not respond to intravenous anesthesia with barbital derivatives. The therapeutic paradox is discussed.

3. Therapy with chlorpromazine and a chelating agent (ethylenediaminetetraacetic acid) was unsatisfactory.

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CASE REPORT

Myasthenia gravis in one monozygotic twin

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THIS REPORT describes monozygotic twins, one of which had myasthenia gravis. The asymptomatic twin was challenged with d-tubocurarine in an unsuccessful effort to uncover latent myasthenia.

Only 4 instances of myasthenia gravis affecting an individual who had a twin were found in reviewing the literature on this disease. Mackay[1] described a female with myasthenia gravis whose twin sister was asymptomatic and showed a normal response to d-tubocurarine. Blood group tests indicated that these twins were fraternal. Wilson and Stoner's[2] Case 1 had myasthenia gravis while an identical twin, erroneously referred to as "binovular" by Kibrick,[3] was normal. The clinical description of the case was not presented, and there was no indication of the method used to establish that the twins were identical. Levin[4] cites Walsh,[5] who saw twin girls, both of whom had myasthenia gravis, but no details are available. Osserman[6] has a set of fraternal twins in his series. The girl, but not her twin brother, was myasthenic.

CASE REPORTS

Case 1. D.G., a 6-year-old Negro boy was seen at the Medical Center Hospital's Neurology Clinic on March 21, 1957, because of drooping of the eyelids.

The patient was entirely well, attending school, and engaging in full activities until one month before his clinic visit, when his grandmother and school teacher observed that his left eyelid drooped. Two weeks later, the right eyelid was noted to droop as well. The drooping was less marked in the morning on arising than later in the day. Vision, speech, and swallowing were not affected. An ophthalmologist was consulted, and some improvement of the ptosis was reported after administration of Prostigmin.

Birth data, other than the fact that he was a twin, were not available. He talked at 2 years of age and performed well in school, where he was described as a "quiet, studious child." No family history of weakness or neurologic or muscular disorders was found on the paternal side. Information from the mother's family was not available because she deserted when the twins, her first children, were 9 months old. The children had been reared by the paternal grandmother.

Examination of the patient showed a well-developed, well-nourished Negro boy with bilateral ptosis that was more marked on the left (Fig. 1). His height was 50¾ in. and weight, 52 lb. He was left handed. Configuration of the skull was normal. The patient was active, alert, and cooperative. Gait was normal. The thyroid was not enlarged. Percusion revealed no mediastinal enlargement. The heart was slightly enlarged to the left by percussion but had a normal sinus rhythm and no murmurs. Abdominal examination revealed no masses. The liver, spleen, and kidneys were not enlarged. Neurologic examination showed intact cranial nerves except for ptosis of the lids and limited extraocular movements. Lateral gaze was limited in both eyes, more so in the left. Upward and downward movements were limited bilaterally as well, The pupils were round, regular, and equal and reacted to light and on near-stimulus. Jaw movements were of good strength. Facial sensation was normal, and the corneal reflexes were intact. Lid

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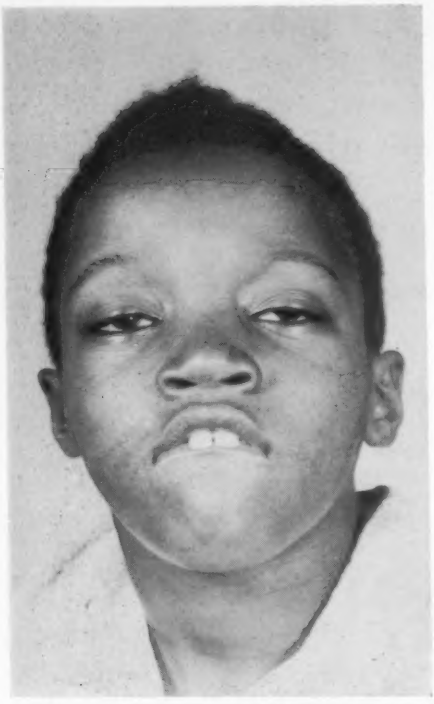

Fig. 1. *(Case 1)* A 6-year old boy with myasthenia gravis

closure was limited. Smiling movements were not impaired, but the facial muscles appeared relaxed. Hearing was normal bilaterally. An active gag reflex was present bilaterally. Swallowing was normal. No dysarthia was discerned. The neck muscles were strong. The tongue protruded in the midline and showed no atrophy. The patient had a strong grip with either hand and had no difficulty climbing on a chair. No muscle atrophy or fasciculations were seen, and there were no abnormal movements. The muscle tone was normal. Reflexes were equal bilaterally. The plantar responses were flexor. Sensation over the extremities and trunk was intact.

The patient was given 10 mg. of Tensilon intravenously, with marked improvement of ptosis and eye movements within one minute. Improvement was transient, lasting a matter of minutes; the patient then reverted to his former state. Prostigmin, 30 mg. every three hours, and atropine, 0.3 mg. twice a day, were prescribed. A chest roentgenogram obtained at the clinic visit revealed widening of the mediastinum and some cardiomegaly. The roentgenologist's impression was persistent thymus with cardiomegaly.

The patient was followed at weekly intervals in the outpatient clinic but showed no improvement in the ptosis or extraocular movements despite adherence to the therapeutic regimen. He was admitted to the hospital in April 1957 for observation while the Prostigmin was increased. The findings on admission to the hospital were the same as those noted in the clinic. Additional Tensilon tests again produced transient improvement of the ptosis. Prostigmin dosage was gradually increased until the patient was taking 60 mg. every three hours Atropine, 0.4 mg., was given concomitantly. However, little or no improvement of the lid ptosis and external ophthalmoplegia resulted, and the patient began to have considerable side reactions in the form of cramps, salivation, and lacrimation. It was repeatedly noted in the hospital that, on arising in the morning or after a nap, the palpebral fissures were widely open, but ptosis recurred within an hour after arising.

Laboratory studies during his hospitalization showed a pseudocholinesterase level of 4.82 units per cubic centimeter, with the normal range being 4.02 to 5.98 units. Serum cholesterol was 190 mg. per 100 cc. The calcium was 11.1 mg.; phosphorus, 5.2 mg.; sodium, 136 mg.; and potasium, 5.5 mg. per 100 cc. The hemogram was normal. The protein-bound iodine was 4.6 μg. per 100 cc. A twenty-four-hour urine collection for creatinine revealed 93 mg. per 100 cc., with a normal range in this laboratory of 100 to 180 mg. per 100 cc. in a twenty-four-hour sample. The creatine excretion was 75 mg. in a twenty-four-hour sample, with the laboratory normal maximum being 60 mg. An electrocardiogram was within normal limits. The roentgenogram of the chest was repeated and showed marked interval decrease in the size of the heart since the previous examination. The only evidence of persistent thymus was a mild convexity of the left cardiac contour just caudal to the arch of the aorta. Blood group studies, finger-ridge

Figure 2

Figure 3

Figure 4

Fig. 2. *(Case 2)* Asymptomatic, identical twin brother
Fig. 3. After intravenous administration of 2 mg. of d-tubocurarine, no curarization is apparent in the normal twin.
Fig. 4. After intravenous administration of 3 mg. of d-tubocurarine to the normal twin, beginning curarization is noted. He was not hypersensitive to this drug.

count, height, weight, and handedness were determined and compared with those of the patient's brother.

Since medication apparently failed to alleviate the patient's symptoms and he was not incapacitated by his ptosis and limited eye movements, it was decided to discharge him on no medication.

On February 11, 1958, a follow-up examination was done. No medication had been taken in the interval. The ptosis had persisted in about the same degree of severity. The left lid still showed more involvement than the right. Although ocular movements remained grossly impaired in all planes in the left eye, they were full in the right eye. The mouth was held slightly open. Still no weakness of the extremities or trunk musculature was noted. The grandmother again affirmed the fact that the patient's eyes were wide open in the morning on arising but tended to droop after about an hour.

On this visit, 60 mg. of Mestinon was administered orally, but no improvement in the ptosis could be detected after thirty minutes.

Case 2. R. G. is the twin brother of the patient described in Case 1. He was asymptomatic. A systemic review and physical examination revealed an apparently healthy, normal child. No weakness of muscles was demonstrable. His height was 50¾ in. and weight was 52 lb., exactly the same as his brother's. He too was left handed. In school, his performance differed from his brother's in that he was more mischievous and active and less studious. His physical features were quite similar to his brother's (Fig. 2). Blood grouping, comparison of finger-ridge count, and the identical height and weight indicated with high probability that the twins were monozygotic[7] (see table).

A curare provacative test was done according to the method of Bennett and Cash.[8] An anesthetist, with respirator available, administered 3 mg. of d-tubocurarine intravenously at a slow rate. After injection of 2 mg., the patient had no difficulty in elevating his lids, and extraocular movements were not limited (Fig. 3). However, after injection of 3 mg., ptosis of both lids was noted (Fig. 4). Since 4 mg.—(3 mg. per 40 lb.)—represented a curarizing dose for this patient,[9] this reaction was well within normal limits and demonstrated that he was not hypersensitive to curare and presumably had no latent tendency to myasthenia gravis when tested. Usually, one tenth of a curarizing dose is adequate to make latent myasthenia gravis manifest,[8] although a small percentage of normal individuals are as sensitive as the average myasthenic patient and some are apparently more tolerant to threshold doses of curare.[10]

In order to determine the probability that a given twin pair is monozygotic or dizygotic,

ANALYSIS OF TRAITS IN PATIENT AND TWIN BROTHER

	Basic relative chance of dizygocity	*Sex*	*Blood groups*					*Finger ridge*	*Height*	*Weight*	*Handedness*
Case 1		Male	O	Ms	ccDee	K—	Fy^a—	P +	110	50 5/8 in.	52 lb.	Left
Case 2		Male	O	Ms	ccDee	K—	Fy^a—	P +	102	50 5/8 in.	52 lb.	Left
Relative chance of dizygocity	2.33	0.5	0.69		0.41	0.37	0.95	0.63	0.85	0.26	0.47
Symbol	poD	p1D	p2D		p3D	p4D	p5D	p6D	p7D	p8D	p9D
pD × poD		× p1D	× p2D		× p3D	× p4D	× p5D	× p6D	× p7D	× p8D	× p9D
pD + 2.33		× 0.5	× 0.69		× 0.41	× 0.37	× 0.95	× 0.63	× 0.85	× 0.26	× 0.47
pD = 0.0075		Probability of being dizygotic = pD/(1 + pD) = 0.0076 Probability of being monozygotic = 1(1 + pD) = 0.992									

information based on objective characteristics that can be quantitated is required. Sex and blood groups are particularly useful, for any difference between the twins makes it certain that they are dizygotic. Other traits, such as finger-ridge count, height, and weight may differ between twins but the greater the difference, the less the probability of monozygocity. The incidence of differences in the measurement of these traits is determined for the two types of twins in a given population by survey, after which it is possible to compute the relative chance of a particular pair being monozygotic or dizygotic.

Smith and Penrose[7] have presented data on the relative frequency of certain traits and the relative chance that twins having these traits in common are monozygotic. Since comparable data are lacking for the population from which our twins came, the values given by Smith and Penrose were utilized in computing zygocity probability, although it is recognized that these data may not apply precisely.

The relative chance of the occurrence of dizygotic twins depends on the population under consideration. The figure given by Smith and Penrose for their population was used and is referred to by the symbol poD in the computation. As soon as additional information about the twins is available, the basic relative chance is modified. The total relative chance (pD) is the product of the independent relative chances of each trait (pD = poD × p1D × p2D . . . pnD) (see table). The probability of being monozygotic is then given by the formula pD = 1/(1 + pD.)

DISCUSSION

The occurrence of myasthenia gravis in an individual who has an identical twin provides a rare opportunity to evaluate hereditary and environmental factors as related to the cause of this condition.

Occasional reports of familial aggregates of myasthenia gravis permit the inference that heredity may play a part in this disease. Such aggregates have been summarized by Walker,[11] Kibrick,[3] Osserman,[6] and Kurland and Alter.[12] They generally fall into several groups: [1] neonatal myasthenia, [2] congenital myasthenia, [3] myasthenia in childhood or adulthood, and [4] myasthenia in offspring of affected fathers.

Strickroot and associates[13] were the first to report a myasthenic infant born to a myasthenic mother. This infant had a weak cry, sucked poorly, and had feeble movements, all of which improved dramatically after Prostigmin was administered. Many such cases have now been described.[6] Levin[4] called these infants "neonatal myasthenics." The weakness in the infant of a myasthenic mother is transient, with symptoms disappearing within a month or two, provided the neonatal period is survived. However, in one patient mentioned by Osserman,[6] symptoms of myasthenia did recur at age 2 and remitted again at age 9. Placental transfer of some "myasthenic factor" from affected mother to infant has been suspected in

these patients, but no such substance has yet been identified. Even if such a factor could be identified, susceptibility to it might conceivably be inherited.

In another group of familial myasthenic patients, symptoms were noted at birth, but both parents were normal.[12] Levin,[4] who described a brother and sister with myasthenia beginning at birth, called such cases "congenital myasthenics" to differentiate them from the neonatal form. Unlike the latter, persons with congenital myasthenia have persistent symptoms that may wax and wane in severity. In one such family,[12] the parents were consanguineous, and a brother and younger sister were myasthenic. The sister had a twin brother[6] who was not myasthenic, although both suffered from epidermolysis bullosa, an hereditary deficiency in elastic fibers of the skin. A male cousin of this family was also myasthenic.

In some familial myasthenic patients with normal parents, symptoms begin in childhood or later in life rather than at birth.[12] These patients follow a course like that of congenital myasthenics or of many with nonfamilial myasthenia.

Finally, several cases of myasthenia in persons whose fathers were similarly affected are known. Noyes[14] has described one such family, but his report antedated the introduction of Prostigmin. Symptoms in the affected members of this family were progressive over many years and did not show the characteristic waxing and waning usually found in myasthenia. Eaton[15] has also treated a father and son who were myasthenic.

No report has been made of a familial aggregate of myasthenia in which the disease occurred in the third generation. Males only, females only, and both genders have been affected in different families. The available reports do not give sufficient data for an opinion regarding the mode of inheritance, and it is well to point out that familial cases are not necessarily genetically determined.

Only one of the identical twins we reported showed myasthenia when examined. The normal twin was not hypersensitive to d-tubocurarine and, therefore, probably did not have latent myasthenia when tested. Although myasthenia may develop in the normal twin later, at the present time, our twinship is discordant for this disease. This experience supports the impression that hereditary factors are not important in the etiology of myasthenia gravis.

Attention was directed to environmental factors in hopes of uncovering a clue to etiology. Nothing in the life pattern of either of the twin boys could be uncovered which appeared very different. They had never been separated from each other for any length of time. If an exogenous factor was responsible for myasthenia gravis in our patient, it was subtle.

Other conditions that were considered in the differential diagnosis in our patient should be mentioned. Progressive external ophthalmoplegia, a form of muscular dystrophy,[16,17] is characterized by ptosis and impaired eye movements and occurs frequently in familial aggregates. However, the muscle involvement in this condition is often symmetric and does not improve with rest. Our patient had asymmetric involvement of the eyelids and extraocular muscles and noted a distinct improvement on awakening and after rest. The response to anticholinesterase medication in myasthenic patients and the lack of such response in patients with progressive external ophthalmoplegia has been a traditional method of differentiating these conditions. Tensilon reversed the ptosis on repeated occasions in our patient. The failure to obtain sustained improvement in eye movements with medication does not necessarily militate against the diagnosis of myasthenia gravis, since weak extraocular muscles often show the least response to anticholinesterase drugs.

Thyrotoxicosis would appear to be ruled out by the normal blood levels of protein-bound iodine and cholesterol and the absence of the usual clinical features of this disease, such as tachycardia and heat intolerance.

Amyotonia congenita, which may produce ptosis, is evident in infancy, and symptoms did not develop in our patient until he was 6 years old.

An abnormality was initially observed roentgenographically in the mediastinum, which was interpreted as being an enlarged thymus. Thymoma or thymic hyperplasia was temporarily entertained as the diagnosis. However, the mediastinal shadow noted on the first chest

film was not present on the subsequent examination. Its significance cannot be explained. The apparent change in heart size between the first and second films is also unexplained.

SUMMARY

The case of a 6-year-old Negro boy with myasthenia gravis is described. He had a normal, monozygotic twin in whom latent myasthenia could not be demonstrated by the curare provocation test. The implications of this example of discordance for heredity as an etiologic factor in myasthenia gravis are mentioned. Examples are cited of myasthenia in familial aggregates, where heredity might have played a part, but information in these reports is too incomplete to permit generalization about genetic mechanisms. No environmental factor was uncovered to explain the development of myasthenia in only one of the twins.

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CASE REPORT

Significance of amplitude asymmetry in the electroencephalogram

Robert J. Strobos, M.D.

FOCAL DEPRESSION or increase of amplitude is seen frequently in the electroencephalogram in association with a slow wave or spike focus. In such instances, the slow wave or spike activity is the most reliable localizing sign and amplitude asymmetry is a relatively minor, corroborating feature. This study deals with amplitude asymmetry as the only abnormal feature in otherwise normal electroencephalograms. We have sometimes encountered this finding in patients who never had evidence of neurologic disease on repeated examinations in the course of several years. In other instances, however, focal amplitude asymmetry had a definite pathologic significance, correctly lateralizing and localizing an organic lesion. This discrepancy led to a statistical evaluation of amplitude asymmetry.

MATERIAL

All the electroencephalograms were recorded with electrode position standardized according to the 10/20 system and with monopolar and bipolar technics. The records were classified after interpretation, and the classification was coded on a punch card; one category of classification was "asymmetry of normal activity." Electroencephalograms were classified in this fashion only when the decrease in amplitude was more than 20% of the amplitude of the contralateral side and was present in more than one lead over the affected region at least 50% of the recording time. Interelectrode distance and electrode resistances were checked when amplitude asymmetry was present. Differences in channel amplification were excluded by switching the recording amplifiers.

The first 200 records with amplitude asymmetry and no other abnormalities were culled from an alphabetical file. It was necessary to go through approximately 5,000 records in alphabetical sequence to obtain these 200 records, an incidence of 4%; 200 normal records were selected in the same fashion. The incidence of normal records was 38%.

The reasons for requesting electroencephalographic examinations may vary in different institutions, and the clinical diagnosis in patients with normal electroencephalograms has a definite bearing on the statistical significance of minor abnormalities. For instance, amplitude asymmetry in a patient with tension headaches has no statistical significance if this clinical diagnosis is encountered with equal frequency in a series of normal records and a series of records with this specific abnormality.

The clinical diagnosis was obtained from the hospital record. More than 90% of these patients had been examined in the Department of Neurology or Neurosurgery.

The records were divided into 3 groups (Table 1): Group I, patients with a diagnosis of psychiatric and other diseases that would usually not cause any abnormalities in the electroencephalogram; Group II, patients with intracranial diseases usually not associated with localized abnormalities in the electroencephalogram; and Group III, patients with intracranial diseases that frequently lead to focal abnormalities in the electroencephalogram. Amplitude asymmetry in these patients would usually

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TABLE 1. DISTRIBUTION OF RECORDS

Group I	*Normal 200 patients*	*Asymmetry 200 patients*	*A*	*AM*	*M*	*MP*	*P*	*H*
Anxiety state	20	14			2		12	
Conversion hysteria	14	9		1	1		7	
Mixed psychoneurosis	6							
Manic depressive psychosis	5	3			1	1	1	
Schizophrenia	5	3					3	
Mental retardation	6							
Headache, cause unknown	31	12			2	2	7	1
Fainting	14	3			1		2	
Tics	2	3			1		2	
Hyperthyroidism	2							
Abdominal pain, cause unknown	1	1					1	
Optic atrophy cause unknown	1							
Cervical radiculitis	1							
Total	108	48	0	1	8	3	35	1
Group II								
Cerebral arteriosclerosis	7	9		1	4	1	2	1
Presenile atrophy	2	3			1	2		
Basilar artery insufficiency	2	2			1		1	
Subarachnoid hemorrhage	1	2			2			
Hydrocephalus		2				1	1	
Pseudotumor cerebri		3			1		2	
Pituitary tumor	2							
Concussion	7	6			2		3	1
Grand mal seizures	30	15			9	1	5	
Parkinson's disease	2	1			1			
Multiple sclerosis	4	2			1	1		
Cerebellar abscess		1			1			
Cerebellar degenerative disease	2							
Cerebellar arterial thrombosis	1							
Migraine	10	8			3	1	3	1
Total	70	54	0	1	26	7	17	3
Group III								
After hemispherectomy		3						3
After temporal lobectomy		3			2		1	
After removal of extracerebral hemorrhage (bone flap)		2			1		1	
Intracerebral glioma		4		1	1	1	1	
Intracerebral angioma		2			2			
Meningioma		1					1	
Extradural abscess		1			1			
Recent infarction (less than 2 months)	8	15			5	4	3	3
Old infarction (more than 2 months)	2	6		1	1		3	1
Internal carotid artery insufficiency		6			1	2	2	1
Subdural hemorrhage		1						1
Extradural hemorrhage		1			1			
Contusion (more than 2 months ago)		7			4		3	
Birth trauma with hemiplegia		11	1	1	1	3	3	2
Encephalitis	1	3	1			1		1
Focal seizures	4	16	2		5	3	4	2
Psychomotor seizures	7	16	1		9	1	4	1
Total	22	98	5	3	34	15	26	15

A=anterior part of hemisphere
M=middle regions
P=posterior part of hemisphere

AM=anterior part and middle regions
MP=middle regions and posterior part
H=whole hemisphere

be considered to have localizing value. It may be noted that, in Group I, the number of normal records exceeds that of the asymmetric records in total as well as in the different diagnostic entities. In Group II, these numbers are approximately equal, while, in Group III, the asymmetric group exceeds the normal group by a statistically significant degree.

The localization of the amplitude asymmetry was classified as occurring in the anterior part of the hemisphere (A), the posterior part of the hemisphere (P), or the middle regions (M). Routine electrode placement is shown in the figure, which has been shaded to indicate the regions considered as A, M, and P. Electroencephalograms with amplitude asymmetry recorded by any or all of the electrodes contained in the shaded area A as compared with homologous electrodes over the contralateral hemisphere were classified under A. The record was classified as H if the amplitude asymmetry was present over the whole hemisphere. If more than one area was involved, the record was classified under a double letter, such as AM or MP. Classification of the various records is reported in Table 1.

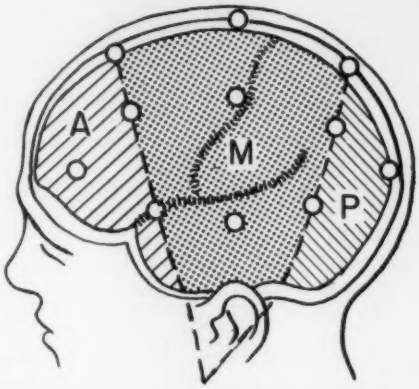
Amplitude asymmetry was more frequently recorded in the posterior than in the anterior hemisphere. The reason may be that posterior asymmetries may occur in normal subjects, which will be discussed later. However, asymmetry is also more easily recognized in the posterior part of the hemisphere because of the distribution of alpha rhythm.

Statistical evaluation was performed by the chi square method. Statistical significance was accepted only when P was 0.01 or less.

RESULTS

No significant difference in sex and age distribution and the percentage of sleep records obtained (Table 2) was found between the groups of normal and asymmetric records.

The incidences of normal and asymmetric records in Groups I and III were compared. The difference in the total number of patients and in all separate categories (such as A and AM) was statistically significant. The same held true if a similar comparison was made between this incidence in Group III and the sum of Groups I and II. However, if Group I and the sum of Groups II and III were compared, the difference was statistically significant for the total number of patients and for all separate categories except P.



Placement of electrodes. Shading indicates the regions considered anterior, middle, and posterior.

This indicates that amplitude asymmetry has a pathologic significance statistically except possibly when it is limited to the posterior part of the hemisphere. Posterior asymmetry was therefore studied more extensively. It was interesting to note that, in the total number of cases, amplitude was depressed on the left side in 121 and on the right in 79. This discrepancy was due to asymmetries limited to the posterior part of the hemisphere, since 59 in the P category were depressed on the left and only 19 on the right, while the incidence for right and left was approximately equal in all other categories. Comparing the distribution of normal records and records with depression in the left posterior hemisphere in Groups I and III revealed no significant difference

TABLE 2

DISTRIBUTION OF AGE, SEX, AND SLEEP RECORDS

	Normal records	*Records with asymmetry*
Males	62%	55 %
Below age 20	29%	34 %
Age 20 - 60	60%	53 %
Above age 60	11%	13 %
Sleep records	48%	37.5%

TABLE 3
DISTRIBUTION OF RECORDS WITH POSTERIOR HEMISPHERE DEPRESSION

	Normal	*Depression on left*	*Depression on right*	*All asymmetric records*
Group I	108	30	5	48
Group II	70	12	5	54
Group III	22	17	9	98

(Table 3). However, a significant difference was noted in a similar comparison between normal records and records with right posterior depression. The records with left posterior depression differed significantly from the total asymmetric group, while the records with right posterior depression did not.

We may, therefore, state that amplitude depression in the posterior part of the hemisphere has a pathologic significance statistically only when occurring on the right side. Depression in the posterior part of the left hemisphere has no pathologic significance statistically.

Unfortunately, we have no data on the handedness of all patients, but it may be assumed that the left hemisphere is dominant in 96%.[1] Depression in the dominant hemisphere, if limited to the posterior part, may be within normal limits.

Amplitude asymmetry in other areas usually indicates an organic lesion, as has been mentioned. It may be noted, however, that there were some records with asymmetry in these other areas in Group I patients showing no evidence of intracranial abnormalities. It might be of importance that, of the 48 Group I records with asymmetry, the depression was present on the left side in 39 and on the right side in only 9. This might indicate that amplitude depression beyond or not limited to the posterior part of the hemisphere occurred on rare occasions in persons without intracranial disease. This depression would usually be found in the dominant hemisphere. The 1 case of amplitude depression in the AM category in Group I was diagnosed as conversion hysteria, and the possibility of a diagnostic error should be considered.

TABLE 4
ACTIVITY OF ASYMMETRY IN SLEEP RECORDS

	Persisted	*Disappeared*
Group I	3	5
Group II	16	9
Group III	34	8

Sleep was recorded in 75 of the 200 asymmetric electroencephalograms. The abnormality persisted during sleep in 53, mostly indicated by asymmetry of spindle amplitude in the affected areas. The sleep record was normal in 22 instances. When we compared the distributions in Groups I and III of the records with persistent asymmetry during sleep and of records in which asymmetry disappeared during sleep, the difference was statistically significant (Table 4). The value of amplitude asymmetry as an indicator of organic lesion thus increases significantly when asymmetry is present or persists during sleep.

In 83 of the 200 patients, the cerebral lesion could be lateralized by positive neurologic findings. In 62, the amplitude depression was on the same side as the lesion but, in 21, was on the contralateral side. Increased amplitude was present over the side of the lesion because of a bone flap in 2 of these 21. The other 19 had various disorders including recent thrombosis, internal carotid artery insufficiency, contusion with hemiparesis, hemiplegia caused by birth injury, astrocytoma, and focal convulsions. The lesion could be lateralized in 35 of the 53 patients in whom asymmetry persisted during sleep, and, in 28 of these, the lesion was on the side of depressed amplitude. Thus, the lesion is more commonly, but not always, on the side of depression.

DISCUSSION

Considerable controversy exists in the literature about the significance of amplitude asymmetry. Gibbs[2] states that minor differences in amplitude are unreliable for purposes of lateralization and often occur in normal subjects. Cobb[3] concurs and states that amplitude asymmetry is not significant unless present to a degree of 50% or more, Williams and Reynell,[4] however, consider amplitude asymmetry of 20% or more as definitely abnormal, even when it occurs in the occipital regions. They never found such asymmetry in a series of 350 electroencephalograms from normal controls. This number may be insufficient. Amplitude asym-

metry was encountered as the only abnormality in only 4% of cases in our total material, which includes patients with and without intracranial disease. It is also noteworthy that Williams and Reynell report unexplained depression of amplitude in cases of psychosis and behavior disorder without neurologic manifestations.

Most investigators[5–9] agree that amplitude asymmetry in the occipital regions is not uncommon in normal subjects, alpha activity then usually being depressed in the dominant hemisphere. Amplitude asymmetry may occasionally involve the temporal and central regions in normal persons.[6–8,10] The pathologic significance of asymmetry increases, however, when more anteriorly located.[11]

Amplitude asymmetry often indicates a lesion and may be of considerable aid in localization. It has been reported as the only significant abnormality in the electroencephalogram in instances of various disorders, including subdural fluid collection, carotid ligation, porencephalic cyst, cranial injury, glioma, angioma, meningioma, chronic abscess, vascular occlusion, and cortical atrophy.[4,9,10,12–15] It is usually assumed that the lesion is in the region of amplitude depression, especially when it occurs in a sleep record.[10] However, exceptions to this do exist,[9,14,15] and our study also indicates that the lesion may at times be present on the side of increased amplitude. This fact makes lateralization difficult. It is sometimes helpful to compare the involved area with immediately adjacent regions to see whether the amplitude is strikingly reduced or increased in the affected area.[15]

SUMMARY

From an alphabetical file, 200 electroencephalograms with amplitude asymmetry as the only abnormal feature and 200 normal electroencephalograms were culled in series. Clinical data on the patients and the localization of the amplitude asymmetry were compared and statistically evaluated. The following conclusions were drawn:

1. Amplitude asymmetry may occur in normal subjects.

2. Depression of amplitude in the occipital region of the dominant hemisphere often has no pathologic significance.

3. Amplitude depression not limited to the occipital region may, on rare occasions, occur in the dominant hemisphere in normal subjects.

4. Amplitude asymmetry usually indicates a lesion if found in regions of the brain other than the dominant occipital lobe.

5. The localizing value of amplitude asymmetry increases considerably when the asymmetry persists during sleep.

6. The lesion is more commonly on the side of depressed amplitude, but this is not invariably true.

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Neurology

BOOK REVIEWS

Recent Neurological Research

edited by A. Biemond, Professor of Neurology, and associates, University of Amsterdam, 330 pp., ill., Elsevier Publ. Co., Amsterdam. Distributed in the United States by D. Van Nostrand Co., Inc., Princeton, N. J. $9.75

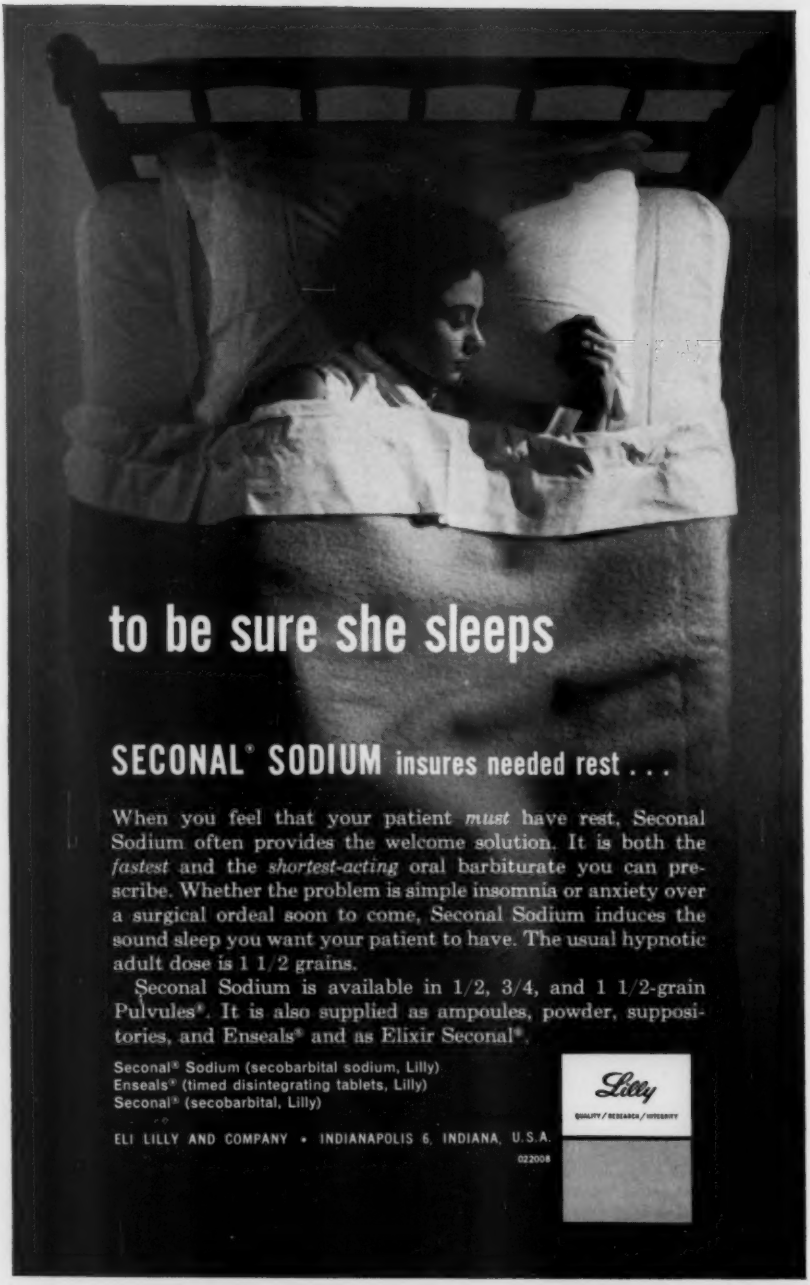
This sturdy volume offers 28 new and original papers on an extraordinary variety of neurologic topics by contemporary Dutch scientists. Since it is not, as the title suggests, a survey of world-wide progress in neurology but rather a rich sampling of that in the Netherlands, it might better have been called "Recent Neurologic Research in Holland." Its publication celebrates the fiftieth anniversary of the founding on October 13, 1909, of the Amsterdam Neurological Society, the members of which now include practically all Dutch neurologists. The uniformly high quality of these contributions honors a great tradition of excellence extending over a period much longer than a mere fifty years.

The reader is at once impressed by the great diversity of topics covered by these articles. There is a wealth of clinical observation on myotonia, the cerebrospinal fluid in neurologic tumors, the effects of stress on diabetes insipidus, the myelopathy of diabetes mellitus, the postconcussion syndrome, aphasia, photogenic epilepsy, and many others. Several experimental physiologic and pathologic studies are included, such as the return of sensation in skin grafts, nutritional degeneration of the ventral horn cells, the pathogenesis of gliomas, and experimental encephalitis. Significant anatomic research is reported, including studies of rhinencephalic connections with the thalamus and the comparative anatomy of the fiber tracts in ungulates and the elephant. Perhaps most striking are several articles touching the philosophy of neurology in its broader aspects, for example, conditioned synapses, cerebral organization and integration, the neurology of consciousness, and the implications of modern neuropsychology, which promises so much as a refinement and expansion of the clinical study of the patient himself.

A second and more reflective impression gained from a reading of this volume concerns the shrewd inferences drawn from simple observations. Here one finds not so much new facts as new and arresting conclusions of broad import. This is neurology of the once familiar but grand style, now too often abandoned in the modern idolatry of instrumental technics. Finally, a carefully selected bibliography, without wasteful padding or provincial bias, makes each article a useful guide to further readings.

The editors and contributors deserve sincere thanks not only for a most valuable collection of significant articles in a notable memorial volume but especially for a pointed reminder of the great contributions to world neurology by Dutch scientists throughout the centuries.

R.P.M.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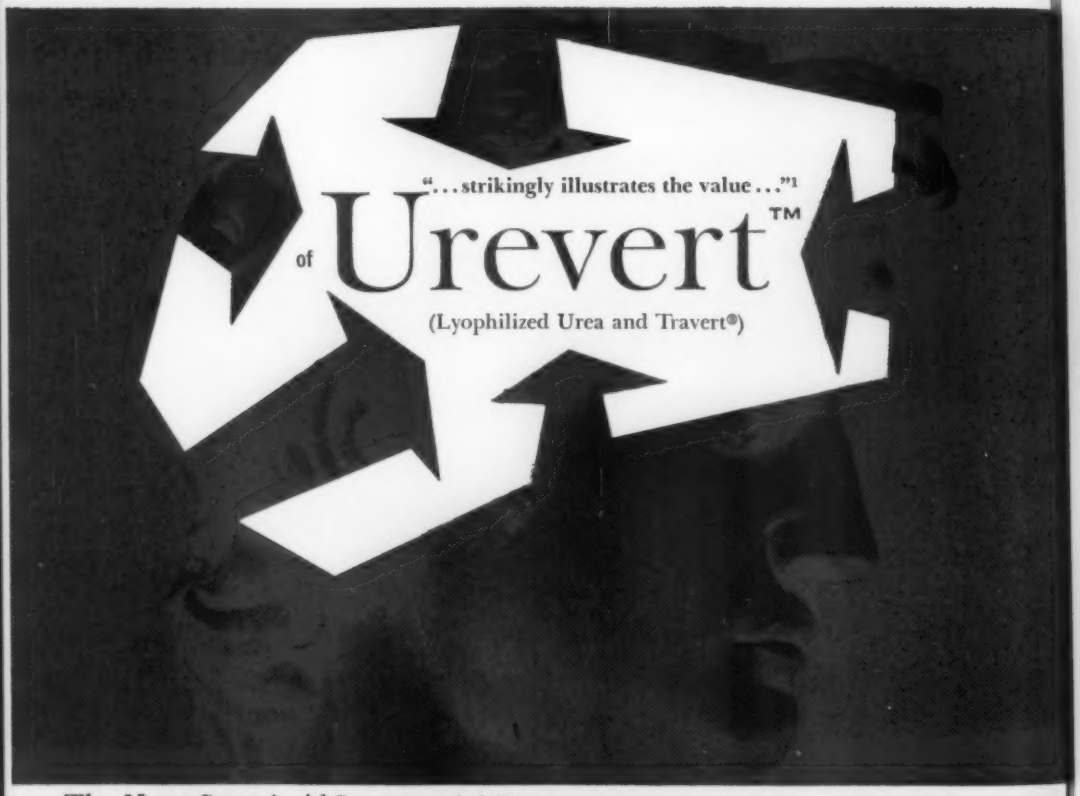

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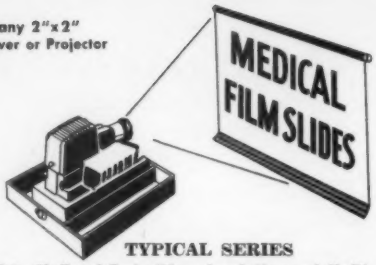

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

AUGUST 1960

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ANA Elects New Officers and Members At its Eighty-fifth Annual Meeting held in the Statler Hotel of Boston, June 13 through 15, the following officers were elected for the year 1960-1961: Harold G. Wolff, President (succeeding Derek Denny-Brown); James L. O'Leary, President-Elect; Harry M. Zimmerman, First Vice-President; and Raymond D. Adams, Second Vice-President. Melvin D. Yahr continues as Secretary-Treasurer and Editor of Transactions and Clark Millikan as Assistant Secretary. Elected to the Council were Derek Denny-Brown (five years) and George A. Schumacher (two years). Augustus S. Rose was appointed representative to the American Board of Psychiatry and Neurology for four years and J. Lawrence Pool as representative to the American Board of Neurological Surgery for six years. The Association elected 9 new active members;* 3 associate members: Stanley M. Aronson, Juan M. Taveras, and Hans-Lukas Teuber; 1 new corresponding member: Shibanosuke Katsuki (Fukuoka, Japan); and 3 honorary members: Philip Bard, John F. Fulton (now deceased), and Sir Russell Brain....Total registrations at the meeting were 629. The Eighty-sixth Annual Meeting of the ANA will be held at the Claridge Hotel in Atlantic City, June 12 through 14, 1961.

Forster Elected President of American Board Francis M. Forster, former AAN President and now Chairman, Department of Neurology, University of Wisconsin School of Medicine, was elected President of the American Board of Psychiatry and Neurology. Dr. Forster has served as a Director of the Board since 1952, representing the American Neurological Association.

Jordan Takes New York Post William K. Jordan, Professor of Neurology at the University of Arkansas School of Medicine, has accepted an appointment as Professor of Neurology at the New York University-Bellevue Medical Center. Dr. Jordan will take over his new post as of August 1, 1960. No successor to the Chair at Arkansas has been named as yet.

Random Notes on AAN Meeting AAN President Augustus S. Rose announces the completion of the revision of the Constitution and Bylaws by Fred Plum and his committee, who will circularize the revisions to all AAN fellows at an early date. Prompt consideration of the revision, when received, is

*Richard G. Berry, Christian Herrmann, Jr., Charles M. Luttrell, Clark T. Randt, Joseph G. Rushton, Robert D. Teasdall, John Nardini, Peritz Scheinberg, and Alexander Silverstein.

urged.... At Miami, 61 active AAN members were elevated to Fellowship.... The AAN membership and placement committees have combined into a single committee of which Maynard Cohen is chairman. Richard L. Masland is chairman of the Subcommittee on Membership and Robert N. Baker of the Subcommittee on Placement. The files of both subcommittees will be kept in the Executive Office in Minneapolis, and the independent function of both Subcommitttes will be integrated by the chairman, Maynard Cohen.... A new AAN committee has been created, the Committee on Problems of Mental Retardation, chaired by Benedict Nagler and having as members Philip R. Dodge, Charles H. Markham, Julius Hoffman, and Charles M. Poser.... AAN Executive Secretary, Mrs. J. C. McKinley, reports the total registration for the scientific sessions of the AAN meeting in Miami Beach was 623. Of these, 431 were members and 192 non-members. This total figure is 13 registrations higher than the 1959 meeting in Los Angeles but lower than the total registrations of 835 at Philadelphia in 1958 and total figure of 683 in Boston in 1957.

New Staff Changes Made at NIH

On July 1, 1960, 4 key changes in the staff of the National Institutes of Health became effective. Joseph E. Smadel, formerly Associate Director for Intramural Research, has become Chief of the Laboratory of Virology and Rickettsiology in the Division of Biologic Standards. Replacing Dr. Smadel is G. Burroughs Mida, previously Associate Director in Charge of Research of the National Cancer Institute, who now is Director of Laboratories and Clinics. Jack Masur, Director of the Clinical Center, has been given additional staff responsibility for policy guidance and program planning as Associate Director for Clinical Care Administration within the Office of the NIH Director. Ernest M. Allen, Chief of the Division of Research Grants, also has been given additional staff responsibility as Associate Director for Research Grants.

Centennial Celebrations Held at Queen Square

Neurologists from 35 countries crowded into a clear-skied London to participate in the Centenary Celebration (1860-1960) of the National Hospital, Queen Square, Bloomsbury June 20 through 25. The scientific program comprised lectures, panel discussions, and demonstrations, including films. Special features were the memorial lectures, held in the Great Hall of the British Medical Association House, to commemorate the names of the National Hospital's founding giants, particularly Hughlings Jackson, William Gowers, and Victor Horsley. The Centennial Oration was delivered by Macdonald Critchley (with Sir Gordon Holmes in the Chair) on "Jacksonian Ideas and the Future with Special Reference to Aphasia." Sir Charles Symonds gave the Gowers Memorial Lecture on "Disease of Mind and Disorder of Brain." Professor Norman Dott presented the Victor Horsley Lecture on "Brain, Movement and Time." Other Queen Square greats of the past to be thus honored were C. E. Beevor (M. Kremer); C. B. Radcliffe (S. P. Meadows);

Brown-Séquard (W. Gooddy); F. E. Batten (J. Marshall); Charles Ballance (T. Cawthorne); and Charlton Bastian (J. H. Patterson). Other "Great Hall" lectures were by M. Alajouanine on the "Principle of Baillanger-Jackson and Aphasia"; by H. Gastaut on the "Post-Hemiplegic Epilepsy as Described by Gowers;" by W. Blackwood on the "Development of Neuropathology at Queen Square;" and by J. N. Cumings on the "Growth of Neurochemistry." There was a panel discussion on "The Future of Neurology," the panel* being made up of clinical neurologists, neuropathologists, physiologists, neurosurgeons, and psychiatrists. The numerous clinical, nursing, and scientific demonstrations were conducted under the auspices of the various departments of the National Hospital and the Neurological Research Unit of the Medical Research Council (E. A. Carmichael, Director).... Many spirited social events livened the evenings of the Centenary Celebrations. The most thickly populated were the Centenary Subscription Dinner held in the Connaught Rooms of Great Queens Street and the Wine and Cheese Party. The latter originally scheduled to be held in Queen Square Garden was forced indoors due to rain, packing the ground floor of the National Hospital to standing room only.

The Society of "Queen Square" Gives Gala Banquet

On Friday evening, June 24, of the Centenary Celebrations, the Chartered Society of "Queen Square" gave, by the kind permission of the Right Honorary the Lord Mayor, an elegant banquet (by invitation) at the Mansion House. About 285 attended. The setting was formal with the traditional routine of evening dress and decorations. Sir Ernest Gowers, son of Sir William Gowers, presided. After a toast to the Queen and members of the Royal Family, Sir Ernest proposed a toast to the Right Honorary the Lord Mayor, Sir Edmund Stockdale, and the Corporation of London and the Sheriffs, which was responded to by the Lord Mayor. These ceremonies were followed by a toast to the National Hospital proposed by Professor Monrad-Krohn with response by Sir John Woods, Chairman of the Hospital's Board of Governors, and a toast to the guests proposed by Dr. Macdonald Critchley and responded to by Mr. Geoffrey Johnson Smith, a member of Parliament, and by Dr. Percival Bailey.

National Conference on Drug Therapy in Neurology Held at Madison

On May 23 and 24, 100 prominent neurologists convened with 8 of the nation's leading biostatisticians to perfect standards for clinical trials of drugs now used in the treatment of neurologic and sensory disorders. The Conference, sponsored by the NINDB Advisory Council, was conducted at the University of Wisconsin under the chairmanship of Francis M. Forster, chairman of the University of Wisconsin Neurology Department.... Richard L. Masland, NINDB Director, opened by stating that the need for better drug evaluation arises from an increase of drugs recently found to be effective against

*Pearce Bailey (Chairman), Raymond D. Adams, S. R. Allison, Sir G. Linder-Brown, Macdonald Critchley, Denis Hill, R. Granite, Michael Kremer, Valentine Logue, W. Noordenbos, and J. D. Spillane. The Right Honorable Lord Cohen of Berkenhead was unable to attend.

neurologic ailments. He said that the present drug evaluation suffers from a lack of standardized criteria, adding that accurate testing of new drugs can be done best with the aid of statistics. Better communication between researchers and testers is needed, Dr. Masland said, to make possible tailor-made drugs for specific diseases.... The conferees pinpointed the problem but divided into 8 panels to propose methods for the most effective evaluation of drugs in 8 disease areas: epilepsy, glaucoma, multiple sclerosis, vertigo, parkinsonism, headaches, muscle diseases, and neuropathies and neuralgias.... Highlight of the conference was a synthesis of the findings of the 8 specialized panels. The conclusions were that methodology studies should be inaugurated to develop accurate definitions and categorizations of disease entities to be studied, to validate available methods of examination of patients, and to establish uniform criteria for drug effectiveness.... The general sessions included talks by a representative of the pharmaceutical industry and the Food and Drug Administration, who defined problems in the testing and evolving of new drugs.

Briefs Charles S. Petty announces the availability to purchase a few sets of 15 slides in each set (slides mounted on plastic film) that are surplus from the slide seminar recently conducted by John A. Wagner, Professor of Neuropathology at the University of Maryland School of Medicine. The cost is $10 per set. Orders should be directed to Dr. Petty, Office of the Chief Medical Examiner, 700 Fleet Street, Baltimore 2, Md. Checks are payable to the Pathology Section, Baltimore City Medical Society... M. G. Peterman will lecture at the University of Madrid where he will receive an honorary degree....E. A. Spiegel is planning a Symposium on Stereotaxis to be held in Philadelphia (October 11, 1961), preceding the Second International Neurosurgical Congress in Washington, D. C., October 14 through 20, 1961....L. H. Gahagan announced that H. W. Dodge, Jr., formerly of the Mayo Foundation Graduate School, has been appointed consultant in neurosurgery at the Beverly Hills Medical Center....Among the early visitors to Europe this summer (AAN members) are Raymond D. Adams, C. G. de Gutiérrez-Mahoney, John R. Green, Brewster S. Miller, H. Houston Merritt, Wilder Penfield, G. Milton Shy, and I. S. Wechsler.... Dr. Mark Callens (Bruges, Belgium) has assumed his duties as Medical Officer to the World Federation of Neurology. He succeeds Charles M. Poser, the first to occupy this post on a year's leave of absence from the University of Kansas, who left on February 15, 1960, to return to Kansas City to assume his academic and professional functions at the University of Kansas and to serve as Editor-in-Chief of WORLD NEUROLOGY. The first edition of WORLD NEUROLOGY (July, Juillet, Juli, and Julio) is out.

Percy Bailey

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[1] K. R. Magee and M. R. Westerberg, Neurology, 9:348, 1959.

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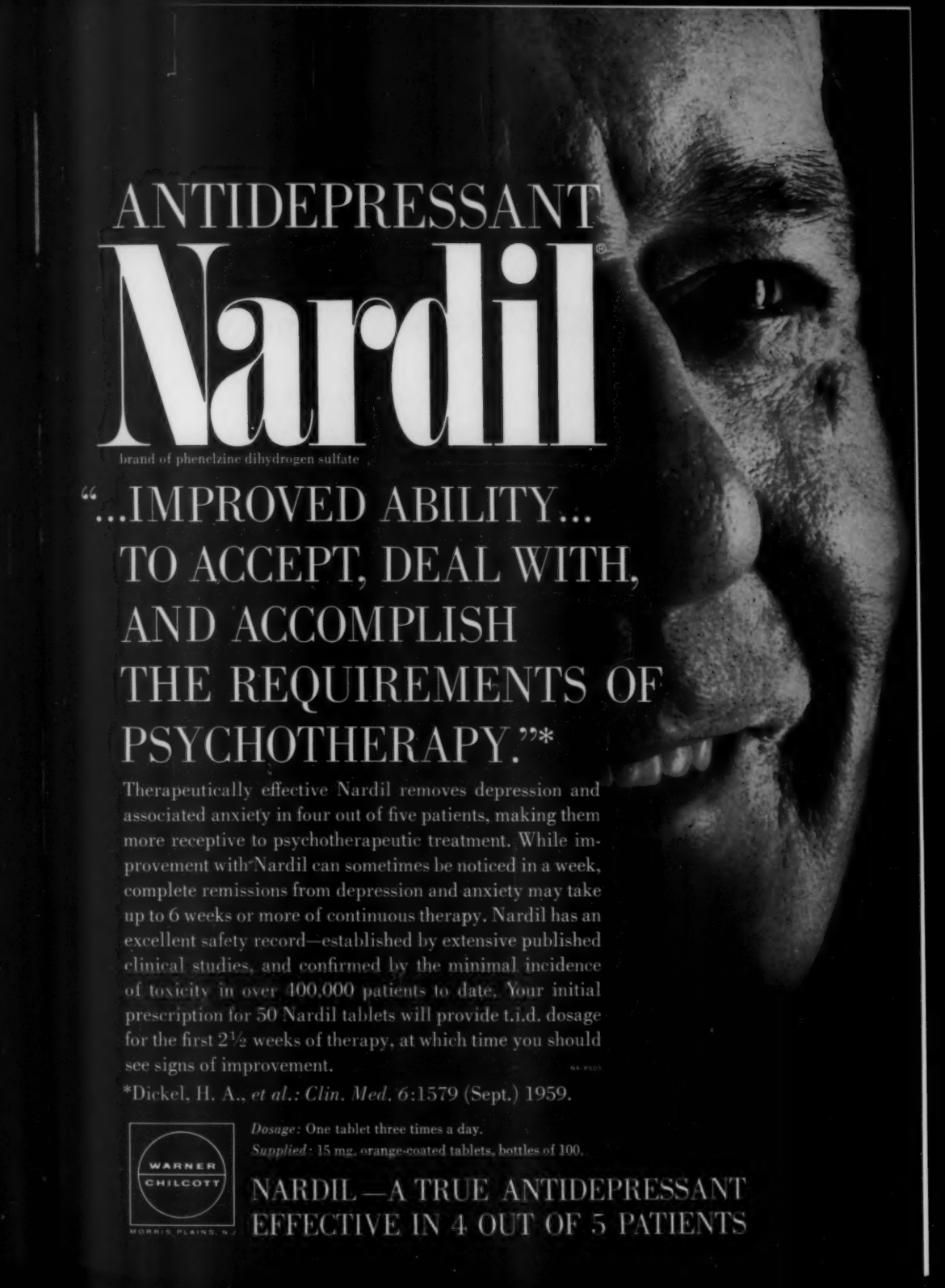

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*Dickel, H. A., *et al.: Clin. Med. 6*:1579 (Sept.) 1959.

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